Clinical Investigation of Portal Hypertension

Katsutoshi Obara
Editor

Springer

Clinical Investigation of Portal Hypertension

Katsutoshi Obara
Editor

Clinical Investigation of Portal Hypertension

Springer

Editor
Katsutoshi Obara
Department of Advanced Gastrointestinal Endoscopy
Fukushima Medical University
Fukushima
Japan

ISBN 978-981-10-7424-0 ISBN 978-981-10-7425-7 (eBook)
https://doi.org/10.1007/978-981-10-7425-7

Library of Congress Control Number: 2018957628

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

Portal Hypertension is a progressive complication due to chronic liver disease, and is responsible for the pathogenesis of most frequent and fatal complications of cirrhosis such as variceal bleeding, ascites, and hepatic encephalopathy.

Over the past two decades, research in the field of portal hypertension has progressed dramatically and has contributed greatly to early diagnosis and optimal treatment of its complications. Particularly in Japan, clinicians working in the field have pioneered a variety of endoscopic techniques for treating esophagogastric varices, some of which have since been largely accepted worldwide.

This book is a comprehensive study of portal hypertension and its complications consisting of 61 chapters focusing in particular on gastrointestinal varices, portal vein thrombosis, refractory ascites, hepatic encephalopathy, and aberrant portal hemodynamics, which have yet to be fully explored. Drawing on the results of research conducted in Japan, the book contains a wealth of information including detailed introductions to safe and effective procedures for preventing recurrence and bleeding of esophagogastric varices.

The main goal of the book is to encourage readers around the world to seek out useful and essential information on both clinical practice and recent research in the field. The book targets a wide diversity of readers ranging from upper-level undergraduate and graduate students to postdoctoral fellows, faculty members and fully-fledged researchers.

I am indebted to the following editors for contributing their experience and making their utmost efforts throughout the development of this book: Dr. Makoto Hashizume, Dr. Shozo Hirota, Dr. Masayoshi Kage, Dr. Norihiro Kokudo, Dr. Shoichi Matsutani, Dr. Naoya Murashima, Dr. Masayuki Ohta, Dr. Isao Sakaida, Dr. Norihiro Watanabe, and Dr. Hiroshi Yoshida (in alphabetical order). I would also like to thank the coauthors, all of whom are Japanese authorities on the board of counselors of the Japan Society for Portal Hypertension. On behalf of the coauthors,

I wish to extend our collective thanks to the publisher Springer Japan, who kindly offered us the opportunity to publish this book as the Japanese Society for Portal Hypertension, And lastly, thanks to Kazuko Abe, my secretary, for her wholehearted support.

Fukushima, Japan Katsutoshi Obara

Contents

Contributors

Editor-in-Chief

Katsutoshi Obara Department of Advanced Gastrointestinal Endoscopy, Fukushima Medical University, Fukushima, Japan

Vice Editors-in-Chief

Masayoshi Kage Kurume University Research Center for Innovative Cancer Therapy, Kurume, Japan

Naoya Murashima Department of Gastroenterology, Mishuku Hospital, Tokyo, Japan

Editors

Kazuko Abe Department of Advanced Gastrointestinal Endoscopy, Fukushima Medical University, Fukushima, Japan

Makoto Hashizume Department of Surgery, Kitakyushu Chuou Hospital Co., Ltd., Fukuoka, Japan

Shozo Hirota IVR Center, Konan Hospital, Kobe, Japan

Norihiro Kokudo National Center for Global Health and Medicine, Tokyo, Japan

Shoichi Matsutani Department of Gastroenterology, Funabashi Municipal Medical Center, Funabashi, Japan

Masayuki Ohta Department of Gastroenterological and Pediatric Surgery, Faculty of Medicine, Oita University, Oita, Japan

Isao Sakaida Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine, Ube, Japan

Norihito Watanabe Department of Gastroenterology, Tokai University Hachioji Hospital, Hachioji, Japan

Hiroshi Yoshida Department of Surgery, Nippon Medical School Hospital, Tokyo, Japan

Part I
Pathology of Portal Hypertension

Chapter 1
Pathology of Liver Cirrhosis in Japan

Makoto Ohbu

Abstract Liver cirrhosis is defined anatomically by the presence throughout the liver of fibrous septa that subdivide the parenchyma into nodules. Cirrhotic nodules often accompany the loss of parenchyma known as parenchymal extinction. Cirrhosis is considered not as an independent disease entity but as a pathologic feature of the terminal stage of various chronic progressive liver diseases. Portal hypertension is the most important complication of cirrhosis, which is caused by obstruction of portal and hepatic veins and arteriovenous shunts in fibrous septa.

Keywords Fibrous septa · Cirrhotic nodule · Vascular obstruction · Parenchymal extinction · Portal hypertension

1.1 Introduction

Cirrhosis is a serious condition where normal liver tissue is replaced by multiple regenerative nodules that are surrounded by fibrous connective tissue (fibrous septum) throughout the liver. Hepatocytes are persistently injured, followed by excessive deposition of extracellular matrix, and regeneration of hepatocytes progresses in an incomplete fashion, resulting in formation of regenerative nodules (Figs. 1.1 and 1.2). The hepatic vasculature is strikingly transformed by the structural changes that occur in cirrhosis. Cirrhosis is considered not as an independent disease entity but as a pathologic feature of the terminal stage of various chronic progressive liver diseases.

M. Ohbu (✉)
Department of Pathology, Kitasato University, Kitasato Institute Hospital, Minato-ku, Tokyo, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_1

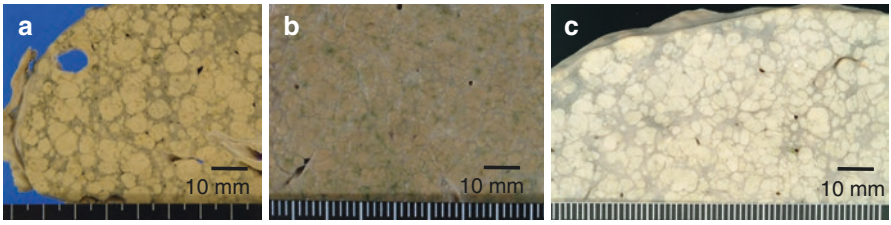


Fig. 1.1 (**a**) HBV-related macronodular cirrhosis. (**b**) Alcoholic micronodular cirrhosis. (**c**) HCV-related mixed nodular cirrhosis

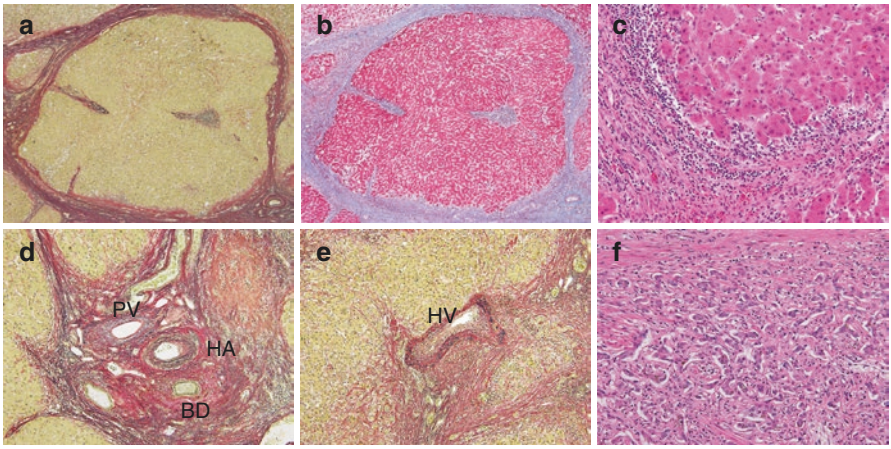


Fig. 1.2 Regenerative nodule separated by fibrous septa in the cirrhosis associated with autoimmune hepatitis. (**a**) Elastica van Gieson stain. (**b**) Azan-Mallory stain. (**c**) Interface hepatitis persists at the periphery of fibrous septum. Obliteration of portal vein (**d**, PV) in the portal tract and hepatic vein (**e**, HV) involved by fibrous septum. (**f**) A nodule is occupied by proliferating bile ductules, which are surrounded by rich collagen fibers. *HA* hepatic artery, *BD* bile duct. (**d**, **e**) Elastica van Gieson stain; (**c**, **f**) hematoxylin-eosin stain

1.2 Definition and Classification

1.2.1 Definition

Cirrhosis is defined anatomically by the presence throughout the liver of fibrous septa that subdivide the parenchyma into nodules [1], as shown in Figs. 1.1 and 1.2. Fibrous septum varies in width. Cirrhotic nodules often accompany the loss of parenchyma known as parenchymal extinction [2].

1.2.2 Classification

1.2.2.1 Classification of Cirrhosis According to Morphology

1. Macronodular Cirrhosis
   Almost all regenerative nodules are composed of large nodules, measuring over 3 mm in diameter (Fig. 1.1a).
2. Micronodular Cirrhosis
   Nodules measure less than 3 mm in diameter (Fig. 1.1b).
3. Mixed Nodular Cirrhosis

Some parts of the liver show micronodular appearance, while other parts show macronodular pattern (Fig. 1.1c). The size of each nodule varies from 1 to 10 mm.

1.2.2.2 Classification of Cirrhosis According to Pathogenesis

It is reported that there are about 400,000–500,000 patients with cirrhosis in Japan, and main etiologic factors are hepatitis C virus in 60% (Fig. 1.1c), hepatitis B virus in 15% (Fig. 1.1a), and alcohol in 15% (Fig. 1.1b) [3]. The annual number of deaths from cirrhosis is about 17,000 [1]. Causes of cirrhosis are shown in Table 1.1.

1. Chronic Viral Hepatitis
   Hepatitis B virus replication often diminishes as cirrhosis advances; therefore, necroinflammatory alteration is attenuated in the fibrous septum, and regenerative nodules get larger, and the fibrous septum becomes narrower in width (Fig. 1.1a). On the other hand, hepatitis C virus replication usually

Table 1.1 Causes of cirrhosis

1. Chronic viral hepatitis, especially chronic hepatitis B and C
2. Autoimmune hepatitis
3. Alcoholic liver disease
4. Nonalcoholic steatohepatitis (NASH)
5. Metabolic disorders
• Hemochromatosis
• Wilson's disease
• Others
6. Biliary cirrhosis
• Biliary atresia
• Primary biliary cirrhosis/cholangitis (PBC)
• Primary sclerosing cirrhosis (PSC)
7. Chronic congestion
• Chronic heart failure
• Budd-Chiari syndrome
8. Cryptogenic cirrhosis

increases as cirrhosis develops; therefore, interface hepatitis gets more severe, and the fibrous septum becomes wider in width (Fig. 1.1c).

2. Autoimmune Hepatitis

   Although autoimmune hepatitis (AIH)-related cirrhosis often lacks pathognomonic findings for AIH, some nodules may show interface hepatitis infiltrated by plasma cells (Fig. 1.2a–f).

3. Alcoholic Cirrhosis

   Pericellular fibrosis precedes the cirrhotic phase in alcoholic liver disease. To keep drinking alcohol suppresses regeneration of hepatocytes, pericellular fibrosis gradually expands, and hepatocytes within fibrous meshwork become atrophic or lost. Thus, central-central or portal-central bridging fibrosis is formed, followed by division of liver parenchyma, nodular formation, and eventually cirrhosis (Fig. 1.1b).

4. Nonalcoholic Steatohepatitis

   Nonalcoholic steatohepatitis (NASH)-related cirrhosis morphologically resembles alcoholic cirrhosis, and it is difficult to distinguish between the two. Fat droplets often disappear or markedly decrease (Fig. 1.3a). There may remain ballooning hepatocytes and pericellular fibrosis in some nodules (Fig. 1.3b).

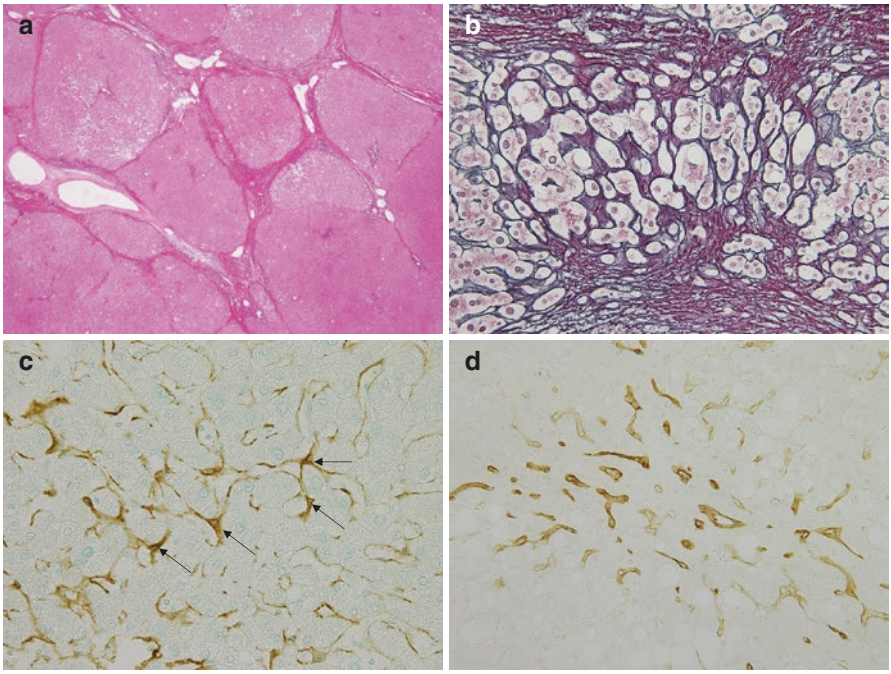


Fig. 1.3 Cirrhosis associated with nonalcoholic steatohepatitis (NASH). (**a**) Nodules vary in size, and fatty change is inconspicuous. (**b**) Ballooning hepatocytes are focally observed with pericellular fibrosis. (**c**) Activated hepatic stellate cells are dispersed in the space of Disse (arrows). (**d**) Capillarization of sinusoids is seen within the nodule. (**a**) Hematoxylin-eosin stain; (**b**) silver impregnation stain; immunostaining for α-smooth muscle actin (**c**) and CD34 (**d**)

Hepatic stellate cells are activated (Fig. 1.3c), and capillarization of sinusoids is shown within a nodule (Fig. 1.3d).

5. Metabolic Disorders

   Cirrhosis caused by Wilson's disease shows characteristic macronodules measuring about 10 mm (Fig. 1.4a). Galactosialidosis is an autosomal recessive lysosomal storage disorder [4] and exhibits micronodular cirrhosis with fat droplet accumulation (Fig. 1.4c, d). Diastase-digested periodic acid (PAS) stain reveals diastase-resistant PAS-positive storage materials in Kupffer cells (Fig. 1.4e).

6. Biliary Cirrhosis

   This type of cirrhosis includes biliary atresia, primary biliary cirrhosis/cholangitis (PBC), and primary sclerosing cholangitis (PSC) [5]. Early phase of PBC is often characterized by "garland" or "jigsaw puzzle"-like regenerative nodules (Fig. 1.5a, b). Nodules become rounded, as the cirrhosis stage advances.

7. Chronic Congestion

   This type of cirrhosis is caused by Budd-Chiari syndrome and right heart failure. Progress in liver fibrosis to cirrhosis is slow, and histology exhibits "reversed lobulation" pattern, in which central-central bridging fibrosis encircles a nodule, and a portal tract locates in the center of the nodule (Fig. 1.5c, d).

8. Cryptogenic Cirrhosis

   There is firm epidemiological data to suggest that NASH should be a dominant cause of cryptogenic cirrhosis in Japan as well as in many areas of the

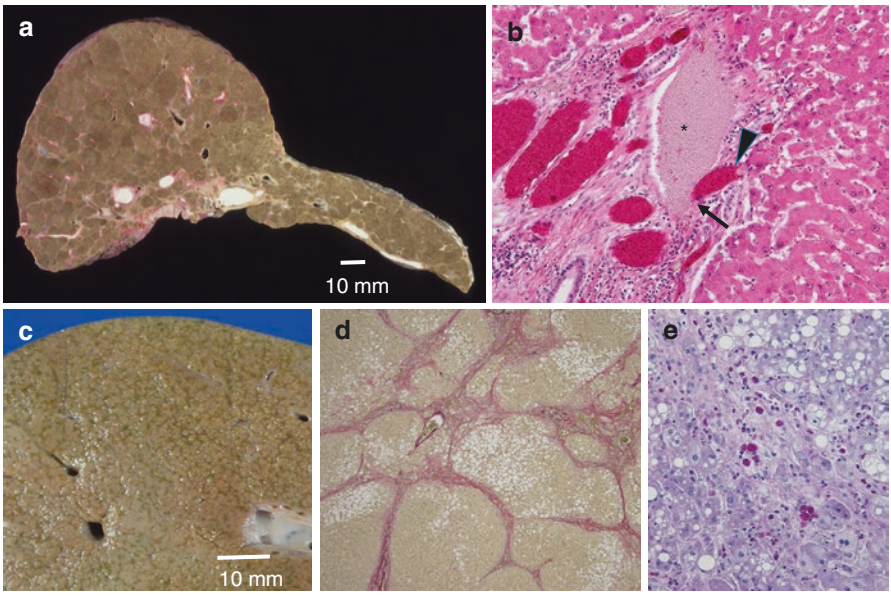


Fig. 1.4 Cirrhosis associated with metabolic disorders. (**a**, **b**) Wilson's disease. Large nodules measuring about 10 mm are shown. White- and red-colored materials are contrast medium injected into portal vein and hepatic artery at autopsy. (**b**) Direct interconnection (arrow) is found between portal vein (asterisk) and arteriolar branch (arrow head). (**c**, **d**, **e**) Micronodular cirrhosis with fat droplet accumulation caused by galactosialidosis. (**d**) Elastica van Gieson stain; (**e**) diastase-digested PAS stain reveals diastase-resistant PAS-positive storage materials in Kupffer cells

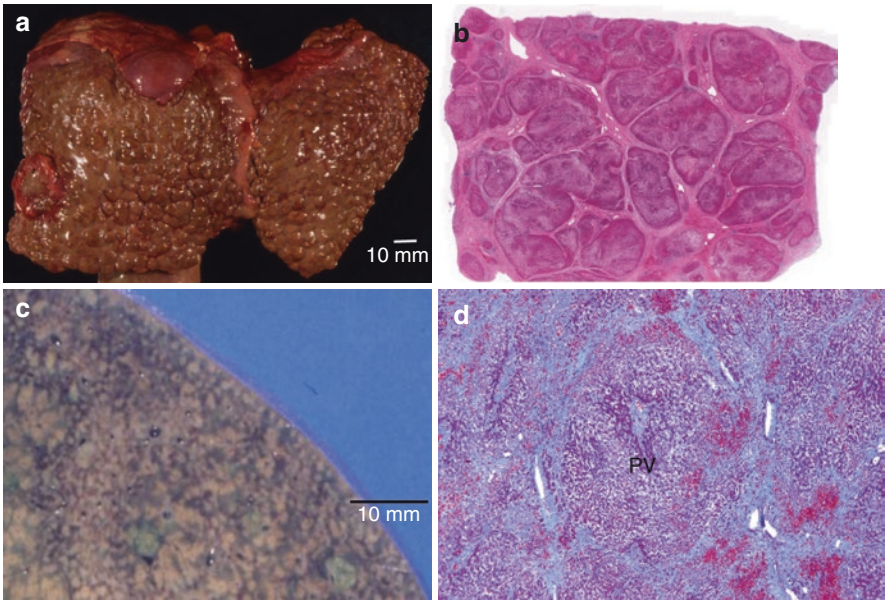


Fig. 1.5 (**a**, **b**) Primary biliary cirrhosis/cholangitis. Regenerative nodules show pathognomonic "garland" or "jigsaw puzzle" pattern. (**b**) Luxol fast blue stain. (**c**, **d**) Congestive cirrhosis. Macroscopic view shows micronodules and surrounding congestion. Histology shows portal tract (PT) locates in the center of the nodule (so-called reversed lobulation), which is encircled by central-central bridging fibrous septa with surrounding congestion

world. Kojima et al. demonstrated that the prevalence rates of body mass index ≥25 kg/m^2, visceral fat area ≥100 cm^2, and type 2 diabetes mellitus were 54.2%, 40.0%, and 54.2%, respectively, in 24 Japanese patients with cryptogenic cirrhosis [6]. Large fatty droplets and other pathognomonic findings for NASH have disappeared in the advanced cirrhotic stage of NASH, and thus this condition is called "burnt-out NASH" (Fig. 1.3). Other potential causes of cryptogenic cirrhosis include burnt-out autoimmune hepatitis and occult viral hepatitis (hepatitis X) [7].

1.3 Secondary Liver Damage Accompanying Progress in Cirrhosis

1.3.1 Alteration of Vascular Channels

1.3.1.1 Capillarization of Sinusoids

In combination with the loss of fenestrations in the sinusoidal endothelial cells and the deposition of aberrant extracellular matrix (ECM) in the space of Disse by stellate cells, the sinusoidal space comes to resemble a capillary [1].

1.3.1.2 Remodeling of Vascular Structures

1. Vascular Obstruction
   Many of the portal veins and hepatic veins are fastened by fibrous connective tissue in septa and obstructed (Fig. 1.2d, e). Such findings are excellently shown by a detailed study of the angioarchitecture of the human liver with graphic reconstructions from thousands of serial sections, which was performed by Matsumoto and colleagues [8, 9]. Mural thrombosis of portal veins and hepatic veins are also found. Regenerative nodules compress hepatic veins.
2. Arterio-portal Shunt and Bypass

Arterio-portal shunt is formed through peribiliary vascular plexus (Fig. 1.4b). In addition, porto-venous or arteriovenous shunt is also formed in fibrous septa. Since blood flows through such shunts, bypasses, and hepatic parenchyma, blood supply to hepatocytes is impaired.

1.3.2 Alterations of Hepatic Parenchyma: Secondary Collapse of Hepatic Parenchyma (Parenchymal Extinction)

Obstruction and thrombosis of portal veins and hepatic veins and blood flow bypassing the liver parenchyma cause acute or chronic circulatory disturbance irrespective of etiology of cirrhosis. A collapsed regenerative nodule is sometimes replaced by bile ductules with indistinct lumen (Fig. 1.2f).

1.4 Pathophysiology of Portal Hypertension Caused by Cirrhosis

1.4.1 Presinusoidal Block

Presinusoidal blood flow resistance rises due to portal vein obstruction in fibrous septa.

1.4.2 Sinusoidal Block

Sinusoidal blood flow resistance increases because of sinusoidal constriction and ECM deposition in sinusoidal wall [1]. Such features are caused by activation of hepatic stellate cells, which produce contractile peptide, endothelin-1 (ET-1), and ECM. ET-1 contracts stellate cells in an autocline loop, resulting in a vasoconstriction.

1.4.3 Post-sinusoidal Block

Hepatic venules compressed by regenerative nodules and fastened in the fibrous septa raise portal pressure.

1.4.4 Arterio-Portal Shunt

Arterio-portal shunt is formed in fibrous septa, and arterial blood flow increases in cirrhosis. Inflow of arterial blood to portal vein through the arterio-portal shunt raises portal flow pressure.

1.5 Regression of Cirrhosis

Cirrhosis has been considered as an irreversible disease until recently. However, it is reported that in a case with elimination of etiology, early phase cirrhosis without advanced vascular remodeling often regresses to the non-cirrhotic phase according to progress in modern therapy. For example, in a viral cirrhosis case from whom hepatitis virus was eliminated, intrahepatic necroinflammatory lesion disappeared, and fibrosis regressed. The main mechanisms for absorption and extinction of collagen fibers are considered as activation of matrix metalloproteinase and inactivation of tissue inhibitor of matrix proteinase-1 [10].

References

1. Crawford JM, Burt AD. Anatomy, pathophysiology and basic mechanisms of disease. In: Burt AD, Portmann BC, Ferrell L, editors. MacSween's pathology of the liver. Edinburgh: Churchill Livingstone Elsevier; 2012. p. 1–77.
2. Wanless IR, Huang WY. Vascular disorders. In: Burt AD, Portmann BC, Ferrell L, editors. MacSween's pathology of the liver. Edinburgh: Churchill Livingstone Elsevier; 2012. p. 601–43.
3. The Japanese Society of Gastroenterology. Guidebook for patients and families about liver cirrhosis; 2010. (In Japanese).
4. Oyanagi K, Ohama E, Miyashita K, Yoshino H, Miyatake T, Yamazaki M, et al. Galactosialidosis: neuropathological findings in a case of the late-infantile type. Acta Neuropathol. 1991;82:331–9.
5. Nakanuma Y, Zen Y, Portman BC. Diseases of the bile ducts. In: Burt AD, Portmann BC, Ferrell L, editors. MacSween's pathology of the liver. Edinburgh: Churchill Livingstone Elsevier; 2012. p. 491–562.
6. Kojima H, Sakurai S, Matsumura M, Umemoto N, Uemura M, Morimoto H, Tamagawa Y, Fukui H. Cryptogenic cirrhosis in the region where obesity is not prevalent. World J Gastroenterol. 2006;12:2080–5.

7. Caldwell S. Cryptogenic cirrhosis: what are we missing? Curr Gastroenterol Rep. 2010;12:40–8.
8. Matsumoto T, Kawakami M. The unit-concept of hepatic parenchyma—a reexamination based on angioarchitectural studies. Acta Pathol Jpn. 1982;32:285–314.
9. Hayashi H. Angioarchitectural changes in a mixed nodular cirrhotic liver. Kanzo. 1989;30:1687–97. (In Japanese with English abstract).
10. Fan TT, Hu PF, Wang J, Wei J, Zhang Q, Ning BF, et al. Regression effect of hepatocyte nuclear factor 4α on liver cirrhosis in rats. J Dig Dis. 2013;14:318–27.

Chapter 2
Pathological Findings for Esophageal Varices

Masahiro Arakawa and Masayosi Kage

Abstract The citing of pathological findings regarding the esophageal varices is uncommon.
Accordingly, the authors report on the histology of esophageal varices including studying failure images of esophageal varices by pathologists and a specialist in endoscopy removing the lower esophagus and stomach at an autopsy en bloc and injecting a liquid into which we mixed gelatin and barium into varicose blood vessels. Also, we compared this histology with endoscopic findings and examined the angioarchitecture of the lower esophagus and discussed the origin of the esophageal variceal rupture.

Keywords Pathology · Esophageal varices · Esophageal variceal rupture

2.1 Introduction

Esophagogastric varices are the most important pathology associated with portal hypertension. Portal hypertension is a pathological condition of hypertension that develops due to abnormalities in the blood circulation through the portal system. This hypertension then leads to the development of secondary symptoms such as esophageal and gastric varices, splenomegaly, and ascites. The term "portal hypertension" thus does not refer to a single disease entity. The background involves various pathologies, and the underlying causes of the hypertension also vary. However, the cause of many of the diseases involved is emphatically determined to be

M. Arakawa
Department of Pathology, Asakura Medical Association Hospital, I
Asakura, Fukuoka, Japan

M. Kage (✉)
Kurume University Research Center for Innovative Cancer Therapy,
Kurume, Fukuoka, Japan
e-mail: masakage@med.kurume-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_2

hypertension due to increased blood flow resistance at sites in the portal system or the hepatic venous system. In the healthy human body, the blood flow in the portal veins is from the lower esophageal and upper gastric region through the left gastric vein and portal veins to the liver. However, if the blood flow through the portal vein is impaired, portal pressure rises and portal vein blood flow increases. The blood flow in the vicinity then reverses in direction, and a hepatofugal collateral circulation develops from the portal vein to the upper gastric and lower esophageal regions. A large volume of blood then flows through the blood vessels in the walls (lamina propria, submucosa) of the upper gastric and lower esophageal regions. The blood vessels dilate and meander, forming protrusions on the surface of the esophagus and resulting in the development of esophageal varices. Here, we report the results of a study conducted jointly by clinicians and pathologists on described pathomorphological findings such as the red color sign observed on endoscopy, with a focus on the histology of the protrusions and rupture sites of varices, which have passed largely unreported.

Prior to the present research, we investigated the relationship between intraportal tumor thrombi and esophageal varices in patients with hepatocellular carcinoma [1, 2] and considered the question of how esophageal varices can best be understood as pathomorphological findings. The presence of tumor thrombi in esophageal varices at that time provided a hint, and in 1980 we began to study varices in earnest using the inspection procedures described below. At that time, endoscopic sclerotherapy was just beginning in Japan, and we were able to study untreated cases and also perform autopsies on cases in the early posttreatment stage. We were fortunate enough to be able to study 50 patients with untreated esophageal varices using a technique in which we injected a contrast agent (described below). Relatively few pathologists appear to have studied esophageal varices up to now, and it is easy to place a dogmatic interpretation on the various pathological findings. However, pathological findings such as bleeding from ruptured esophageal varices match clinical findings on emergency endoscopy, particularly the detailed findings from emergency endoscopy reported by Makuuchi et al. [3], which we consider provides some degree of objectivity.

2.2 Procedure for Inspection of Varices

Briefly, the stomach and esophagus are removed en bloc (up to the mid-esophagus) at the time of autopsy. Barium that has been added to gelatin is warmed to a liquid state and infused into the left gastric vein (gastric coronary vein) which supplies the varix. The specimen is chilled immediately after infusion and fixed in 10% formalin. An image is obtained using a Softex X-ray system, and the specimen is dehydrated in an ascending alcohol series and cleared with methyl salicylate solution. Macroscopic photographs are taken for examination. This method enables the specimen to be examined in a state more closely resembling the status during life [4–6]. Figure 2.1 shows a macroscopic image, soft radiograph, and transparent preparation

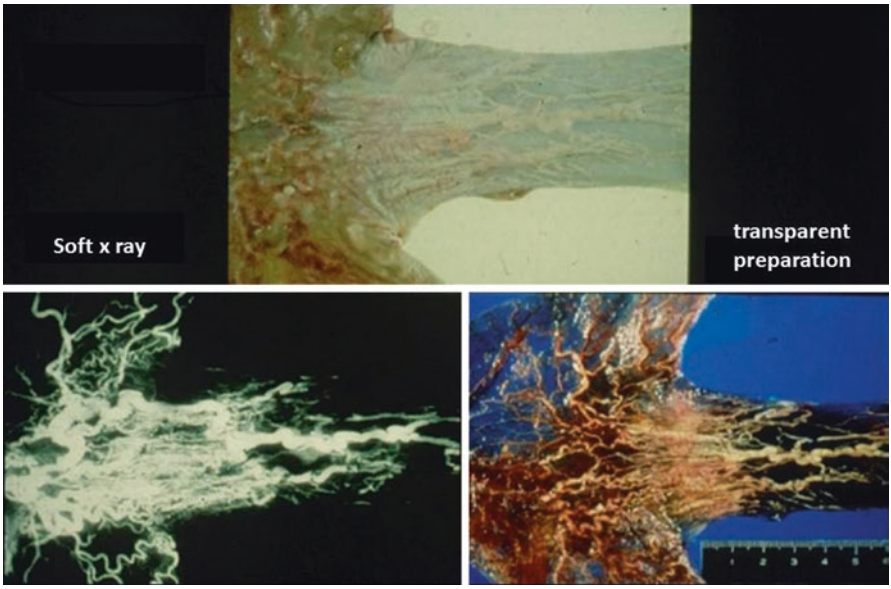


Fig. 2.1 Upper panel: Gelatin-barium injection preparation. Lower left: soft radiograph. Lower right: transparent preparation

for an esophagus and stomach that had been removed from a patient with esophageal varices and infused with the contrast agent. Problems associated with this type of examination involve the infusion pressure. However, our method is considered to apply almost no pressure to the varix, because the resected margins of the esophagus are opened, and the infusion of fluid does not increase the pressure.

In greater detail, our procedure is as follows. First, phosphate-buffered saline is injected into the left gastric vein, and the blood in the vessel is washed out. Next, 20% gelatin-barium (warmed to a liquid state) is infused. This infusion is stopped as soon as barium flows out of the cross section of the resected esophagus, and the organ is chilled in ice and fixed in ordinary formalin. After 1–2 days, macroscopic photographs are taken, and the specimen is sequentially dehydrated in an ascending alcohol series of 70, 80, 90, and 100%. The specimen is kept immersed in the absolute ethanol for 5–7 days, and after sufficient dehydration has been achieved, a transparent preparation is prepared using methyl salicylate. Only the blood vessels are visible in the transparent preparation, and the specimen is photographed after thorough macroscopic inspection prior to tissue specimen preparation. The key advantage of this procedure is to allow macroscopic observation, and tissue specimens can be prepared from sites identified as appropriate. This method of preparing tissue specimens allows accurate determination of the site of bleeding and subsequent detailed findings corresponding to endoscopic findings. For the excision of the histopathological specimens, the transparent preparations are returned to the original formalin-fixed specimens, and for the excision of microscopic specimens of

the esophagus, the specimens are cut into round slices so that all blood vessels at cross sections of the walls can be visually examined.

2.3 Vascular Architecture of the Normal Human Esophagus

Kegariesin [7] and Butler [8] investigated the vascular architecture of the normal human esophagus by injecting substances such as dyes into blood vessels and tracking their routes. However, it was not until 1966 that DeCarvalho [9] published a readily understandable detailed schematic of the routes of these blood vessels. That article surpassed its predecessors in terms of both detail and accuracy. However, we noted an error in the resulting schematic, in that Zone 3 (by DeCarvalho) showed a direct connection between the veins of the lamina propria and the netlike venous plexus immediately underlying the epithelium. However, our own studies of the relationship between those vessels have shown that the netlike venous plexus covers the entire esophagus and connects with the veins of the lamina propria at various sites. In the palisade zone (described below), fine blood vessels (reported as *sudare*-like veins) run almost in parallel over the entire circumference in the lamina propria, whereas only two to three fine blood vessels run in the submucosa. Our results in this regard are consistent with the findings of DeCarvalho.

2.4 Vascular Architecture in Esophageal Varices

Figure 2.2 presents our schema for the vascular architecture of the esophageal varices. This shows the palisade and truncal zones, in which three to four dilated, meandering vessels run, and their transitional area, termed the "critical area." The palisade zone cannot be accurately measured, but its length is within the range of 1.5–4.0 cm and is 2–3 cm in many patients. Figure 2.3 shows a macroscopic transparent preparation from a representative patient and the associated cross-sectional histological images. Vianna et al. [10] reported in 1987 regarding this classification and described a similar vascular architecture to that explored in our report. They described the area in which *sudare*-like veins ran as the palisade zone, and we therefore adopted the same expression. This zone represents the point of contact between the portal system and the systemic circulatory system. The lower boundary starts from the transitional area of the esophagogastric mucosa, while the upper boundary extends to the *hiatus* of the diaphragm and broadly corresponds to the abdominal esophagus. In a normal human body, blood in this area flows into the portal vein on the side of the gastric cardia, and in the neck the blood ascends from the esophageal veins through the azygos or semi-azygos vein to the superior vena cava.

Diseases that cause portal hypertension exhibit vascular resistance inside and/or outside the liver, and stasis of blood flow occurs in vessels such as the splenic vein and superior and inferior mesenteric veins, which are part of the portal system.

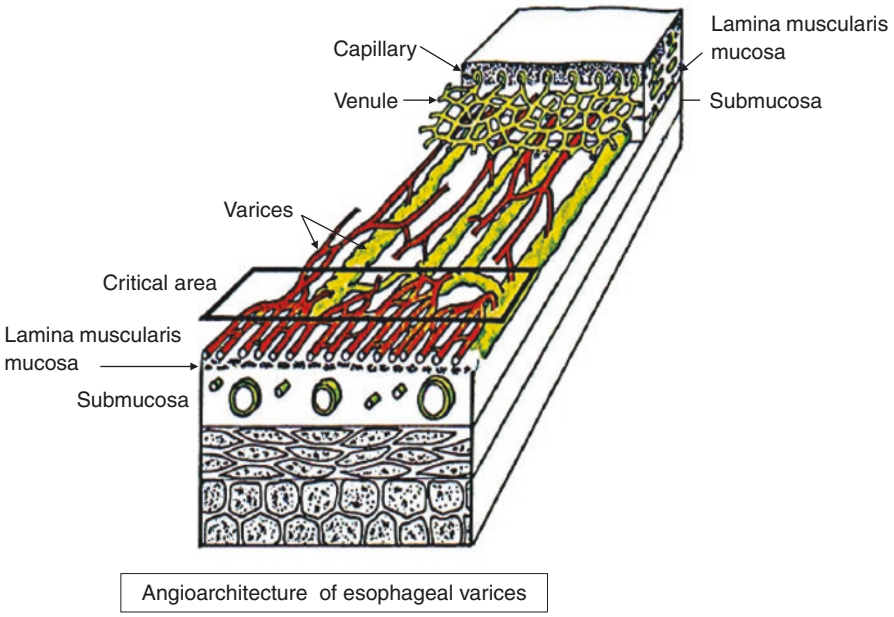


Fig. 2.2 Our schema of Zones 2–4 in the lower esophagus in portal hypertension with varices formation

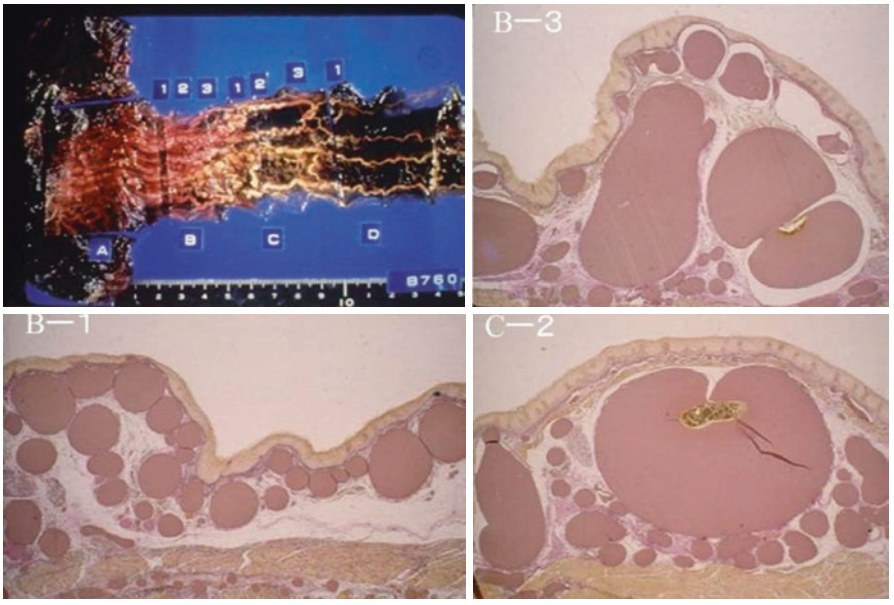


Fig. 2.3 The original transparent preparation (upper left) showing the various zones from which the corresponding sections were taken. B1, palisade zone; B3, transitional zone; C2, truncal zone ×20

If the stasis is severe, blood flow seeks escape in another direction. This is the hepatofugal collateral circulation, in which paths are opened to blood vessels such as the gastric and esophageal veins, the hemorrhoidal vein, and the abdominal wall veins.

Development of a hepatofugal collateral circulation leads to changes in the normal esophageal vascular architecture. That is, blood that was previously flowing from the palisade zone to the gastric cardia and then to the gastric coronary vein (left gastric vein) flows in a retrograde manner from the gastric coronary vein to the palisade zone. In this situation, the main blood circulation in the palisade zone flows in the lamina propria, and in the initial stage, the blood flows from the submucosa of the gastric cardia to the lamina propria of the palisade zone. The flow is then toward the blood vessels in the submucosa of the esophageal varices, but dilation of the blood vessels in the lamina propria gradually becomes more pronounced. As vascular resistance increases, the blood flow connecting the submucosa of the cardia to the submucosa of the esophageal varices (truncal) becomes the main flow. Schematically, these events lead to the blood flow changes shown in Fig. 2.4. Histological examinations of the palisade zone reveal the dilated blood vessels around the entire circumference of the lamina propria, but at the same time dilated blood vessels are also seen in the submucosa. Close inspection of these vessels run-

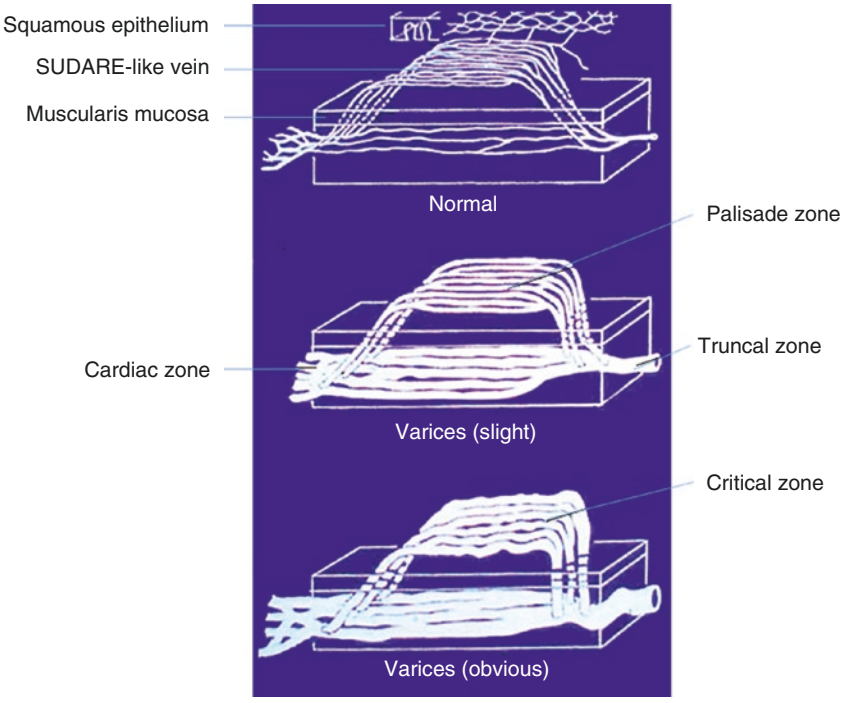


Fig. 2.4 Schema of dilated esophageal veins. The normal vein image has been slightly modified from the image of Dr. De Carvalho (1966)

ning in the submucosa reveals that, in addition to the inherently present vessels, other blood vessels come to run in the submucosa and are surrounded by the broken muscularis mucosae. On the basis of this finding, we surmised that those vessels do not represent new vessels per se but rather blood vessels that have been pushed into the submucosa from the lamina propria [11].

In summary, the vascular architecture of the esophagus in the palisade zone and other zones in patients with portal hypertension is characterized by large blood vessels (veins) in the submucosa, and although similarities exist between them, the basic vascular architecture differs. Such changes in the routes of blood vessels have never been reported, and this may be because only dilated vessels stand out in antemortem endoscopic findings.

Next, the critical area warrants attention. As was noted above, this area is the region in which ascending, dilated, meandering submucosal veins transition from the palisade zone to the truncal zone (Fig. 2.4). Clinically, the area in the lower esophagus that contains many ruptured vessels has been referred to as the critical area, and we have adopted this name since the transitional area contains many ruptured varices. In this area, many blood vessels, including the blood vessels seen in the lamina propria throughout its entire circumference and the previously mentioned blood vessels running in the submucosa, all flow into three to four blood vessels in the submucosa. This results in striking vascular piles. In addition, if we examine at cross sections of this region histologically, since vascular piles are apparent in patients with advanced varices, pronounced protrusions into the esophageal lumen are evident, and thinning of the epithelium of the esophagus is often seen (Fig. 2.3).

Since the vascular piles in the lamina propria flow into the blood vessels of the submucosa, sharp curves of the vessels are formed, resulting in elevated hemodynamic load. For these reasons, the blood vessels in this area are more likely to rupture. Of course, if erosion and/or inflammation are present in the esophageal mucosa, rupture in some sections of the esophageal varices may occur. However, in consideration of the vascular architecture, the palisade zone, which is rich in blood vessels in the lamina propria, may also have a high risk of rupture. Three to four variceal veins can be observed under modalities such as endoscopy as veins in the submucosa from the transitional area toward the oral side, narrowing with increasing proximity to the oral side.

These blood vessels in the submucosa anastomose with the other veins and sometimes pass through the muscle layer and anastomose with the paraesophageal veins. At the oral side from the transition area, the blood vessels of the lamina propria are markedly fewer in number compared with those of submucosa, and the possibility of rupture is considered small.

A cross section of the esophageal wall shows the presence of veins in the lamina propria over the submucosal veins (lumen side), and the netlike venous plexus immediately underlying the epithelium is seen over the lamina propria (representing a point of difference from the schema of DeCarvalho). Fine blood vessels running vertically from the venous plexus can be seen in the epithelium, and fine blood vessels can also be seen in the epithelium. As the varices develop further, the piles

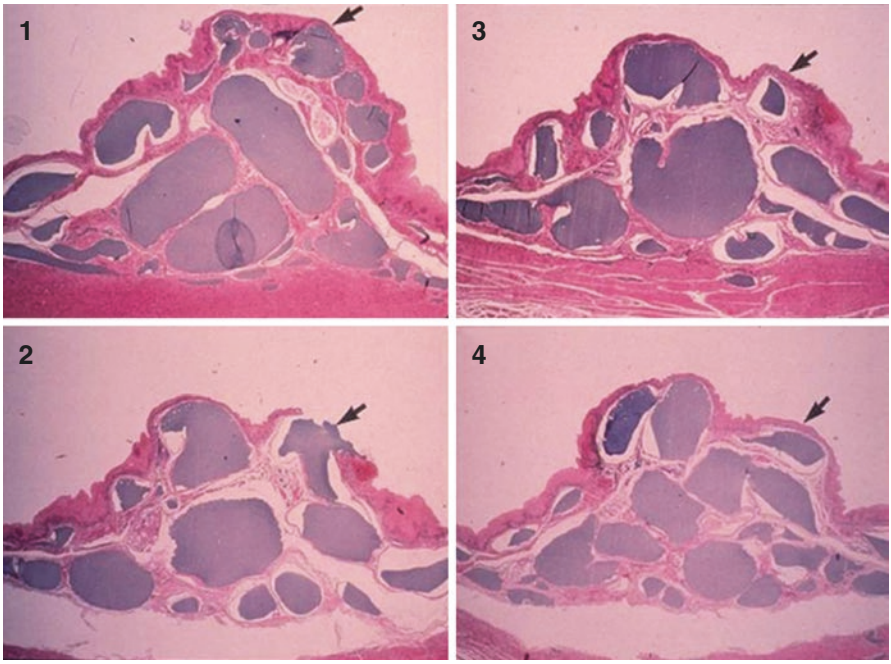


Fig. 2.5 Histological findings in serial sections made around the bleeding point. Section 2 is the bleeding point, and Sections 1, 3, and 4 are from areas near Section 2

of these blood vessels increase, the epithelium becomes thinner, and there the color sign becomes visible on endoscopy. Severe piles of varices are seen most frequently in the critical area. In fact, the bleeding point was identified in this area in all eight untreated patients we examined [4, 5]. If we inspect serial sections around the bleeding point, we find this corresponds to the red color sign (Fig. 2.5).

2.5 Bleeding Point of Esophageal Varices

The lower esophagus has been reported as being the most common site of bleeding of esophageal varices [12, 13], and while this has been readily confirmed clinically, there has been little confirmation from pathological studies of the site. Emergency endoscopy can now be performed safely, and findings such as the modes and sites of bleeding and the presence of post-bleeding fibrin clotting can now be elucidated [3]. However, anatomicopathological confirmation of the bleeding point at autopsy remains difficult, and this will become even more difficult in the future as most patients now undergo treatment before death.

Our group works in collaboration with clinicians, enabling the study of autopsy cases with ruptured esophageal varices by performing both more careful observa-

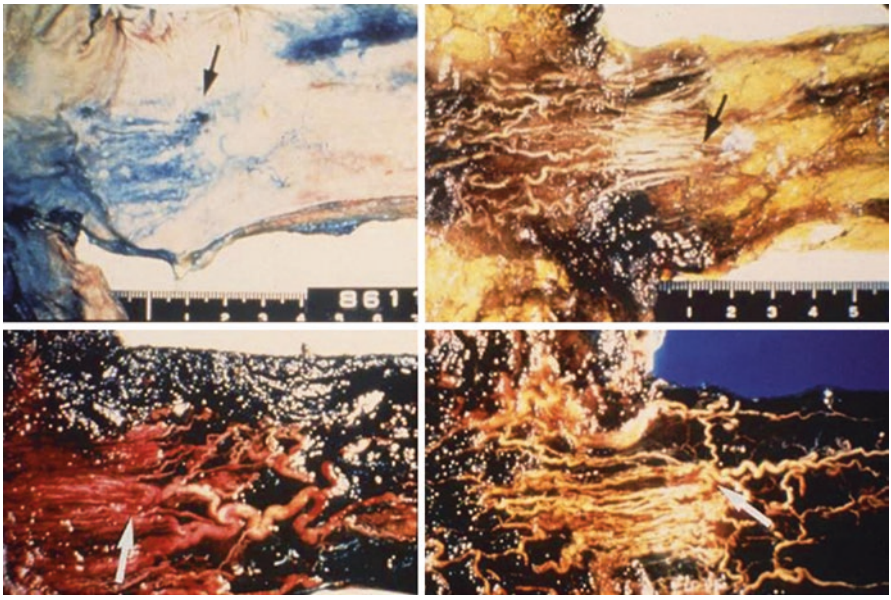


Fig. 2.6 The point of bleeding (arrows) from esophageal varices in four cases

tion of the esophagus and of inspection of sites of contrast agent leakage following infusion. Even in cases with no findings of contrast agent leakage, we prepare a serial tissue section of sites that macroscopically appear to be potential sites of rupture and inspect them microscopically. Our results have shown that the site of rupture bleeding is almost always in the region designated as the critical area (Fig. 2.6). Moreover, even in cases showing no leakage, the rupture hole can be histologically confirmed and is occluded by a blood clot [14]. This has also been elucidated from endoscopic observation of rupture sites. Our study of serial sections taken from around the rupture hole revealed a thinned squamous epithelium caused by blood vessels in the lamina propria. In addition, whether rupture bleeding is caused by elevated venous pressure or by inflammation has long been in question. Our pathological studies of the histogenesis of rupture cases have suggested that elevated venous pressure is a more likely cause of such ruptures.

2.6 Comparison with Endoscopic Findings

In 1980, the *General Rules for Recording Endoscopic Findings on Esophageal Varices* [15] was published in Japan, and reports stating that the red color sign (one of the endoscopic findings) is very closely related to bleeding gained attention. As a result, attention was focused on the pathology represented by the red color sign; however despite much discussion regarding histological findings, no conclusions

were able to be reached. The reason was that the collected tissues were unable to capture the varices as aneurysms. Later, the 1991 update of these General Rules [16] added emergency endoscopic findings, including findings of rupture bleeding.

To elucidate the relationship between the red color sign and the histological change, we then cut a large number of sections, mainly from the critical area, of ten patients with untreated esophageal varices who had been infused with gelatin-containing barium and who showed antemortem endoscopic findings of a rupture hole. This pathology was described, and endoscopic and histological findings were compared. On the basis of those results (Fig. 2.5), we were able to prove that the red color sign on endoscopic observations was consistent with findings of a thinned epithelium due to vascular piles in the lamina propria. In addition, images around the rupture hole in serial sections showed that the ultimately thinning epithelium partially corresponded to the rupture hole.

2.7 Summary

We applied a technique using a contrast agent in patients with untreated esophageal varices and reported pathomorphological images of variceal rupture mainly at the anatomical site of rupture bleeding that had not previously been elucidated. In addition, we compared endoscopic findings with histological findings and clearly showed histological images corresponding to the red color sign. We also discussed the mechanisms of variceal rupture.

References

1. Arakawa M, Koga M, Kage M, et al. Pathomorphological study on primary liver cancer—relationship between tumor thrombus and esophageal varices. Acta Hepatol Jpn. 1979;20:941–7. (Jpn).
2. Arakawa M, Kage M, Matsumoto S, et al. Frequency and significance of tumor thrombi in esophageal varices in hepatocellular carcinoma associated with cirrhosis. Hepatology. 1986;6:419–22.
3. Makuuchi H, Machimura T, Sugihara T, et al. The bleeding points of esophageal varices and the time course of their morphologic changes. Endosc Dig. 1989;1:1031–7. (Jpn).
4. Arakawa M, Noda T, Fukuda K, et al. Clinicopathological studies of esophageal varices—the structure of blood vessels in esophageal wall. J Jpn Soc Gastroenterol. 1983;80:2339–46. (Jpn).
5. Noda T. Angioarchitectural study of the esophageal varices. With special reference to variceal rupture. Virchows Arch A Pathol Anal Histopathol. 1984;404:381–92.
6. Arakawa M, Kage M. The anatomy and pathomorphology of esophageal varices. In: Okuda K, Benhamou JP, editors. Portal hypertension. Clinical and physiological aspects. Tokyo: Springer; 1985. p. 415–28.
7. Kegaries DL. The venous plexus of the esophagus. Its clinical significance. Surg Gynecol Obstet. 1934;58:46–51.
8. Butler H. The veins of the esophagus. Thorax. 1951;6:276–96.

9. DeCarvalho CAF. Sur“I’angio”G. Architecture veneuse de la zone de transition. Oesophagogastrique et son interpretation fonctinelle. Acta Anat. 1966;64:125–62.
10. Vianna A, Hayes PC, Mosecso G, et al. Normal venous circulation of the gastroesophageal junction. A route to understanding varices. Gastroenterology. 1987;93:876–89.
11. Arakawa M, Kage M, Oukubo K, et al. Angioarchitecture of lower esophagus in portal hypertension cases. J Jpn Soc Gastroenterol. 1991;88:1336–40. (Jpn).
12. Dagradi AE, Stempine SJ, Owens LK. Bleeding esophago-gastric varices -an endoscopic study of 50 cases. Arch Surg. 1966;92:944–7.
13. Orloff MI, Thomas HS. Pathogenesis of esophageal varix rupture. Arch Surg. 1963;87:301–7.
14. Arakawa M, Noda T, Fukuda K, et al. Clinicopathological studies of esophageal varices. Histological findings of ruptured esophageal varices and its relationship to endoscopic findings. Gastroenterol Endosc. 1985;27:191–8. (Jpn).
15. Japanese Research Society for Portal Hypertension. The general rules for recording endoscopic findings on esophageal varices. Jpn J Surg. 1980;10:84–7.
16. Japanese Society for Portal Hypertension. General rules for recording endoscopic finding of esophageal varices (1991). World J Surg. 1995;19:420–2.

Chapter 3
Anatomy of the Spleen and Pathology of Hypersplenism

Masayoshi Kage, Reiichirou Kondou, and Toshirou Ogata

Abstract The functions of the spleen are hemofiltration, purification, and immune function, but for a long time, the spleen has been said to be a mysterious organ with many unknown features remaining to be elucidated, such as the pathology of hypersplenism in portal hypertension.
In this chapter, firstly, the structure and function of the spleen are explained. In addition, the pathomorphology of splenomegaly in patients with liver cirrhosis and idiopathic portal hypertension (IPH) is explained. Liver cirrhosis and IPH share the histology of chronic congestive lesions, but differences have also been reported.

Splenectomy and partial splenic embolization (PSE) to treat hypersplenism in cirrhotic patients are reviewed. Splenectomy and PSE have provided many benefits, such as improvement of hypersplenism, portal hypertension, and liver function, completion of interferon therapy and liver cancer treatment, and improvement of immunity, which may contribute to the prognosis of cirrhotic patients. Generally, splenectomy is considered to reduce immunocompetence and leads to infection susceptibility, but improvement of immunocompetence by splenectomy is rather expected in cirrhotic patients.

Keywords Spleen · Pathology · Portal hypertension · Liver cirrhosis · Idiopathic portal hypertension · Hypersplenism · Splenectomy

M. Kage (✉)
Kurume University Research Center for Innovative Cancer Therapy, Kurume, Fukuoka, Japan
e-mail: masakage@med.kurume-u.ac.jp

R. Kondou
Department of Pathology, Kurume University, School of Medicine, Kurume, Fukuoka, Japan
e-mail: kondou_reiichirou@kurume-u.ac.jp

T. Ogata
Department of Surgery, St. Mary's Hospital, Kurume, Fukuoka, Japan
e-mail: ogacchi@med.kurume-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_3

3.1 Introduction

The spleen is located below the left diaphragm and contacts with the pancreatic tail. It is the size of a child's fist in adults and weights 80–120 g. It is slightly larger in females than in males and atrophies with aging. The spleen is a host-defense organ present between the systemic circulation and portal system, and it is the biggest lymph apparatus in the human body. The spleen has immune response functions such as the production of lymphocytes and monocytes. In addition, it functions as a filtration apparatus processing red blood cell waste and foreign bodies in the circulation and blood pool.

When portal hypertension persists for a prolonged period due to liver cirrhosis, the spleen shows splenomegaly by passive congestion and functional abnormality, which is generally termed hypersplenism. In this chapter, the anatomy and histology of the spleen are reviewed, and the splenic pathology in portal hypertension is explained.

3.2 Structure and Function of the Spleen

3.2.1 Vascular System of the Spleen

A schema of vascular system of the spleen is shown in Fig. 3.1. The artery enters the spleen through the splenic hilum, branches in a dendritic pattern, distributes in the trabecula of the spleen (trabecular artery), penetrates the white pulp as the central artery, and becomes the penicilliary artery branching like a brush tip. The central artery branches in the white pulp and ends in an opening in the marginal zone of the white pulp described below. The end of the artery branching from the penicilliary artery ends in an opening in the connective tissue of the splenic cord (open vascular network). Blood which flows into the splenic cord passes through the slit between the endothelial cells forming the splenic sinus and flows into the splenic sinus. The splenic sinus shows a wooden barrel-like structure comprised of endothelial cells lined up in parallel with the major axis direction like barrel boards. Red blood cells pass through the gap between the endothelial cells of the splenic sinus from the splenic cord and enter the splenic sinus. The splenic sinus is the starting point of the portal venous system in the spleen. It reaches the splenic hilum through the trabecula of the splenic vein, becomes the splenic vein, and flows into the portal vein.

3.2.2 Splenic Histology

Normal splenic histology: The spleen is comprised of the red and white pulps and marginal zone [1] (Fig. 3.2).

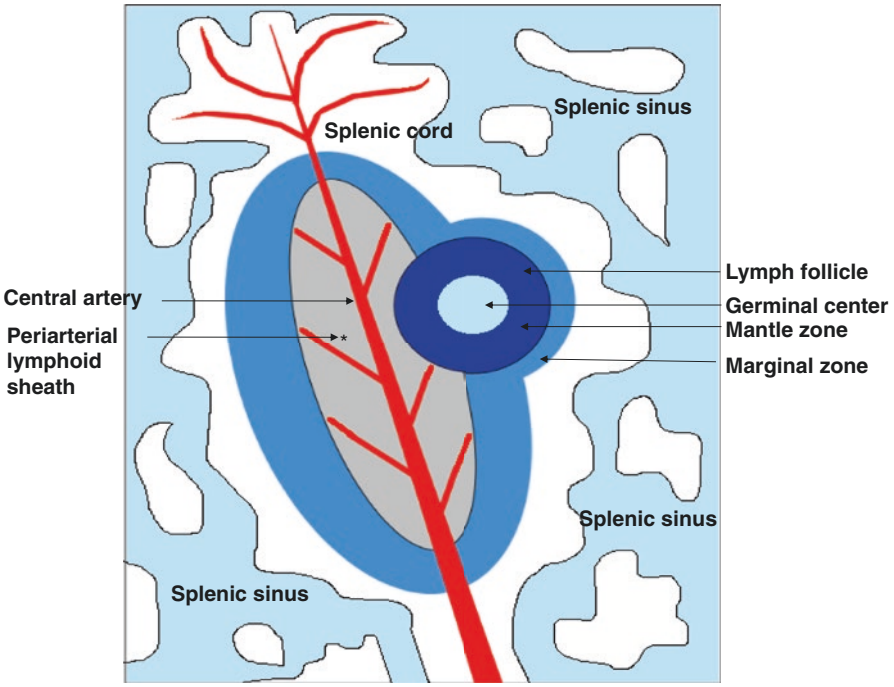


Fig. 3.1 A schema of the histology of the normal spleen. *PALS* periarterial lymphoid sheath

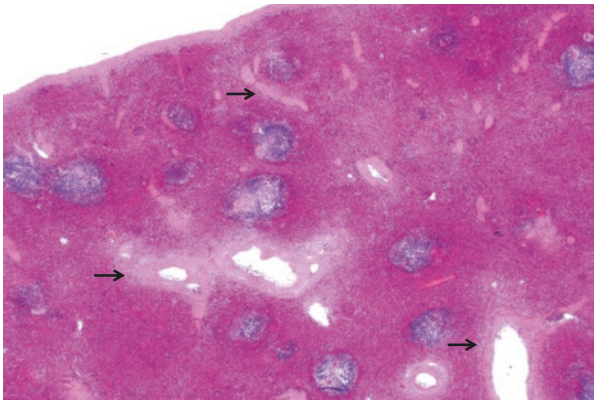


Fig. 3.2 The histology of the normal spleen (HE stain)

The red pulp is comprised of the splenic cord and splenic sinus. The splenic cord is present between the splenic sinuses and comprised of netlike arranged reticulum cells and reticular fibers forming a network organization structure. As described above, in the splenic cord, the penicilliary artery ends in an opening, and red and white blood cells and macrophages flow out from it (Fig. 3.3).

The white pulp is a lymphatic tissue, and it is comprised of two regions: a periarterial lymphoid sheath (PALS, assembly of lymphocytes surrounding the central

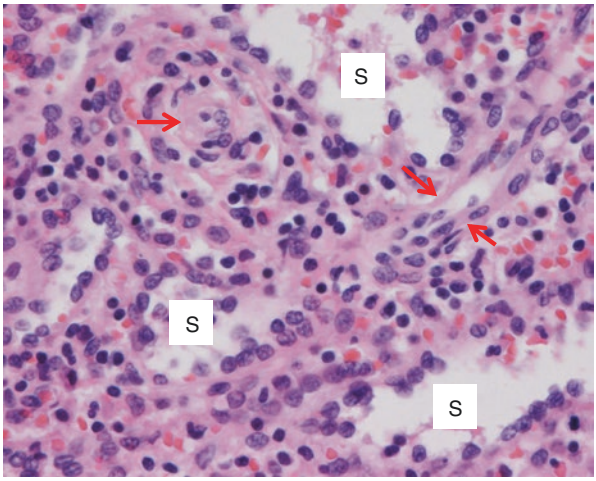


Fig. 3.3 The histology of the red pulp of the normal spleen. The red pulp consists of the splenic cord and sinus (S). The end of the penicilliary artery (arrow) is open, and the erythrocytes flood in the splenic cord. The erythrocytes enter into the splenic sinus from the splenic cord through the slits between the endothelial cells. *S* splenic cord (HE stain)

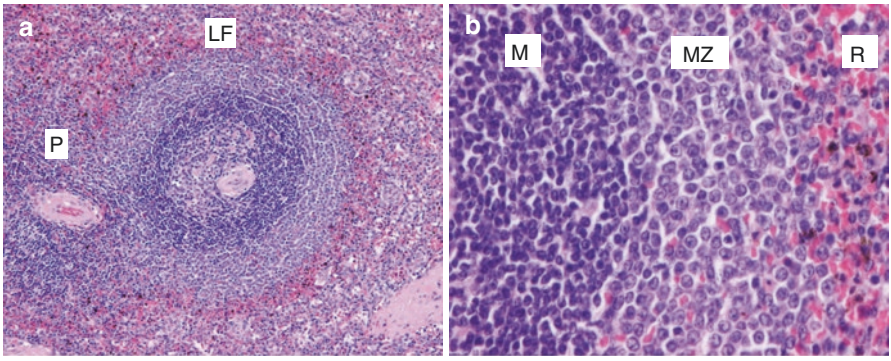


Fig. 3.4 The histology of the white pulp and marginal zone (MZ) of the normal spleen. (**a**) White pulp consists of lymph follicle (LF) and periarterial lymph sheath (PALS). *LF* lymph follicle, *P* PALS. A LF has a germinal center in the center. A mantle zone surrounds the germinal center like donuts. The marginal zone surrounds LF. (**b**) Magnified image of (**a**). The mantle zone is composed of strongly basophilic small lymphocytes. The MZ has medium-sized lymphocytes with clear and rich cytoplasm, compared with those of MZ. *M* mantle zone, *MZ* marginal zone, *R* red pulp (HE stain)

artery) and a lymph follicle (LF) (Fig. 3.4a). PALS is a region in which T lymphocytes surround the central vein in a sheath pattern, and it is dependent on the thymus. LF is an assembly of B lymphocytes, and the germinal center is present in the center. The germinal center appears whitish on HE stain. The mantle zone is present as if it surrounds this germinal center in a donut shape. The mantle zone appears strongly basophilic and intense purple, different from the germinal center.

The marginal zone (MZ) surrounds the white pulp in a zone pattern and contacts with the outer red pulp. MZ appears whitish compared with the mantle zone because the lymphocyte morphology is different between the mantle zone and MZ. Lymphocytes in the mantle zone lack cytoplasm, while those in MZ are moderate-sized and contain relatively rich cytoplasm (Fig. 3.4b). MZ is constituted with a network organization in which lymphocytes and macrophage are mixed. MZ is considered a lymphocyte-recirculating region.

3.3 Splenomegaly in Portal Hypertension

When portal hypertension occurs, the spleen swells due to passive congestion. Correlation between the portal pressure and spleen weight in a rat liver cirrhosis model has been reported, but no correlation was confirmed in humans [2]. The portal pressure was normal in a case with marked splenomegaly, and it has been reported that splenomegaly accompanying portal hypertension is proliferative splenomegaly accompanied by an increase in the splenic blood flow [3]. Mechanism of splenomegaly in cirrhotic patients cannot be fully explained by portal hypertension-induced congestion only. Liver cirrhosis-induced congestive spleen; an increase in splenic venous blood flow; vasoactive substances released from the spleen, such as endothelin; and an influence of cytokines on the liver are involved in portal hypertension.

3.4 Splenic Pathology in Portal Hypertension: Hypersplenism

3.4.1 Pathological Findings of the Spleen in Cirrhotic Patients

In the spleen in hepatic cirrhotic patients, the percentage of the red pulp area increases, and that of the white pulp decreases relatively.

In the red pulp, dense outgrowth of new splenic sinuses, narrowing of the splenic cord, and reticulum cell proliferation are observed. Swelling of endothelial cells occurs throughout the splenic sinus. When fibrosis progresses in the red pulp and trabecula of the spleen, the normally clear contour of the trabecula of the spleen becomes unclear.

Changes in the white pulp vary among the cases: marked atrophy of LF occurs in some cases (Fig. 3.5a), whereas the germinal center is clear and swollen in others (Fig. 3.5b). In our study on the spleen in 17 cases of liver cirrhosis [4], LF was large in some cases, but it was generally small, or the size irregularity was marked in about half of the cases. In addition, T lymphocytes in PALS decreased in number. Moreover, atrophy and obscuration of MZ and a decrease in the number of MZ B lymphocytes were noted in cirrhotic patients with a marked increase in the splenic

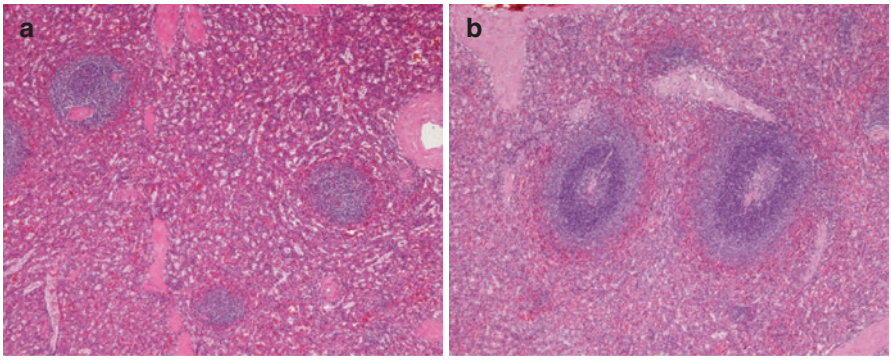


Fig. 3.5 The histology of the spleen in liver cirrhosis. (**a**) A case of liver cirrhosis with markedly atrophic white pulp. The germinal center of white pulp and marginal zone are unclear. The red pulp stands out, and the splenic sinuses are increased. (**b**) A case of liver cirrhosis with prominent white pulp. The germinal center is enlarged, and the marginal zone is broad and distinct. The red pulp stands out, and the splenic sinuses are increased. The red pulp shows fibrosis, and the outline of the trabecula is not clear (HE stain)

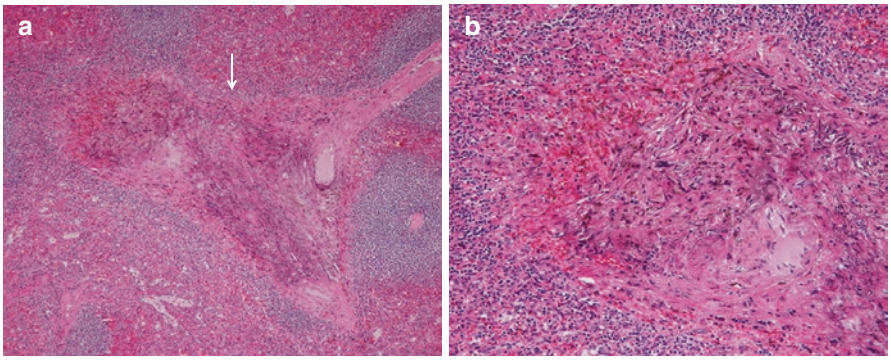


Fig. 3.6 Gamna-Gandy (G-G) body in chronic passive congestion in the spleen of liver cirrhosis. (**a**) The trabecula (arrow) shows a G-G body formed after hemorrhage. (**b**) Magnified image of (**a**). G-G body is calcification with hemosiderin deposition, showing mixed various color of black, purple, and brown (HE stain)

weight. MZ is located in a region contacting the opening of blood flow, being the front line of the immune system in the white pulp. For these changes in the white pulp and MZ, association with immunologic abnormality, which is often observed in portal hypertension patients, has been suggested [3].

In the spleen, congestion may cause hemorrhage in the splenic capsule and trabecula. In these hemorrhagic foci, calcification of hemosiderin occurs with time as foci become old and shows a characteristic histology termed Gamna-Gandy (G-G) nodules. G-G nodules serve as an index of oldness of lesions (Fig. 3.6a, b). Hemorrhage due to congestion occurs in various organs, but G-G nodules are specific histological change not observed in the other organs.

3.4.2 *Pathological Findings in the Spleen in Idiopathic Portal Hypertension (IPH)*

Idiopathic portal hypertension (IPH) is defined as a disease causing portal hypertension accompanied by splenomegaly and anemia excluding diseases with well-known causes, such as liver cirrhosis and extrahepatic portal venous obstruction, and its pathogenesis has not yet been identified [5]. IPH patients often develop huge splenomegaly, and its weight is generally heavier than the splenic weight in cases with liver cirrhosis. Previously, the spleen in IPH was mainly considered simple portal hypertension-induced secondary congestive splenomegaly; however, many recent studies suggest involvement of certain immunologic abnormality as a cause of splenomegaly [3, 6]. Moreover, Sato et al. [7] reported enhanced expression of nitric oxide syntheses in splenic lining cells in IPH, which may be one of the causes leading to abnormal portal hemodynamics.

Specificity of the splenic pathology in IPH has been discussed for a long time; however, no conclusion has been reached. The main histopathological findings of the spleen in IPH patients are similar to those in cirrhotic patients: expansion of the red pulp, marked hyperplasia of the splenic sinus, and narrowing of the splenic cord. Fibroadenia is one of the histopathological characteristics of the spleen in IPH (Fig. 3.7); this is also observed in cirrhotic patients. Although the histology in IPH is similar to that in liver cirrhosis, differences have also been pointed out [3, 8]. Nakagawa et al. [3] concluded that the splenic histology in IPH is different from that in liver cirrhosis, and the basic histological feature is splenitis accompanied by structural destruction of the red pulp. As the basis to regard splenitis as the cause, they pointed out that splenic cord infiltration by various inflammatory cells, such as lymphocytes, plasma cells, macrophages, and neutrophils, is observed in the spleen in early-stage IPH. They assumed that, in IPH, splenitis develops in association with hyperemia of the splenic artery, and splenic sinus hyperplasia occurs mainly in the

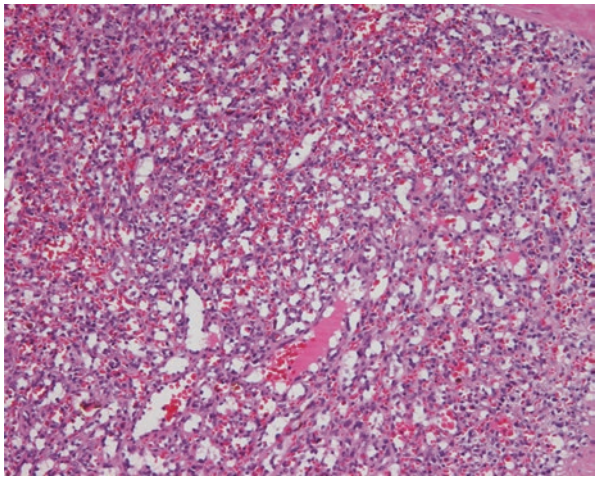


Fig. 3.7 The histology of the spleen in liver idiopathic portal hypertension. The red pulp shows fibroadenia, characterized by compact proliferation of splenic sinuses, narrowing of the splenic cords, and increased deposition of reticulin fiber. The germinal center of white pulp and marginal zone are prominent (HE stain)

splenic arterial system, leading to splenomegaly. Changes in the white pulp in the early disease stage of IPH are considered reactive hyperplasia of LF, and lymphocyte activation is considered a characteristic phenomenon of IPH.

The spleen is also involved in the cause of elevating portal pressure in IPH. Occluded intrahepatic peripheral branch of the portal vein and an increase in splenic blood flow are considered the main causes of portal pressure elevation in IPH. As a cause of the latter, Maesawa et al. [9] attach greater importance to irregular slit expansion between rod cells forming the splenic sinus among ultrastructural findings of the spleen in IPH. Slits in the splenic sinus create blood flow resistance when splenic cord blood (released from the peripheral artery) flows into the splenic sinus. It is assumed that slit expansion reduces blood flow resistance, resulting in increasing blood flow in the spleen.

3.5 Treatment of Hypersplenism with Splenectomy and Partial Splenic Embolization (PSE)

3.5.1 Splenectomy for Hypersplenism

Although splenectomy for hypersplenism has long been a standard treatment, clinical cases and study reports on splenectomy for liver cirrhosis-associated hypersplenism have recently increased.

The main objectives of splenectomy are (1) improvement of hypersplenism-associated thrombocytopenia and subsequent completion of interferon (IFN) therapy and hepatocellular carcinoma treatment [10–13] and (2) improvement of portal hypertension to induce gastroesophageal varices and hemorrhagic tendency [14]. In addition, improvement of the liver function by splenectomy has been reported as follows: (1) release from a state of portal hypertension, (2) removal of liver regeneration-inhibitory factors such as TGF-βin the spleen, (3) reduction of bilirubin load from destroyed red blood cells shortened by hypersplenism, and (4) potentiation of liver regeneration-promoting factors such as platelet-derived serotonin.

In our experiment using cirrhotic rats [15], increased splenic TGF-β is regarded as a cause of liver fibrosis. After splenectomy, TGF-β in the sera significantly decreased, and fibrosis of liver tissue histopathologically remitted (Fig. 3.8). In humans, we also reported that liver fibrosis remitted after splenectomy in some cases [11].

Although splenectomy has many clinical benefits as described above, we found the therapeutic efficacy of splenectomy is attenuated by necroinflammation of the liver in cirrhotic patients [16].

Improvement of the immune function after splenectomy has been reported [17]. In liver cirrhosis, portal hypertension causes congestive splenomegaly resulting in hypersplenism. Although it is termed “hypersplenism,” it is unclear whether or not the spleen function is really enhanced. It was reported that pitted cells in peripheral blood, which are regarded as an index to evaluate the spleen function, significantly

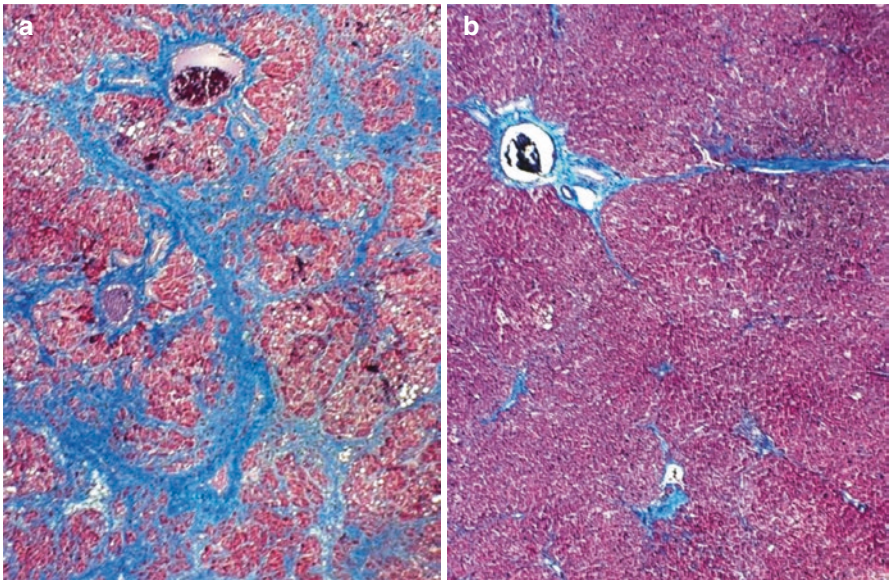


Fig. 3.8 Histological changes of the liver in cirrhotic liver after splenectomy in experimental rat model [15]. (**a**) The histology of the liver without splenectomy, showing liver cirrhosis with severe fibrosis. (**b**) The histology of the liver after splenectomy, showing decreased fibrosis and disappearance of liver cirrhosis (Azan stain)

increased showing reduced splenic function in liver cirrhotic patients, and no significant association was noted between spleen hypofunction and infection [18]. It has recently been reported that the functions of T and B cells in the spleen are reduced in cirrhotic patients, and splenectomy improved the Th1/Th2 balance and antitumor effect [17]. Hashimoto et al. [19] investigated the influence of the spleen on T cells in patients with hepatitis C-associated liver cirrhosis and observed that IFN-γ production by T cells recovered after splenectomy, recovering Th1 response of $CD4^+$ T cells.

In addition, reductions of white blood cells and neutrophils were significantly recovered. Generally, it is considered that splenectomy reduces immunocompetence, leading to infection susceptibility, but we consider that splenectomy for cirrhotic patients may improve the immune function [10, 11].

3.5.2 Partial Splenic Embolization (PSE) for Hypersplenism

Partial splenic embolization (PSE) is another treatment option to improve hypersplenism. Similar to the effects of splenectomy, in addition to increasing platelets, PSE is reported to improve liver function, hypersplenism, portal hypertension, and gastroesophageal varices [20].

References

1. Schmidt EE, Macdonald IC, Groom AC. Microcirculatory pathways in normal human spleen, demonstrated by scanning electron microscopy of corrosion casts. Am J Anat. 1988;181:253–66.
2. Misawa T. Induction of experimental splenomegaly with portal hypertension in rats with liver cirrhosis. Nihon Shokakibyo Gakkai Zasshi. 1991;88:2653–62.
3. Nakagawa S. The spleen—idiopathic portal hypertension. Clin All Around. 1984;9:1781–6.
4. Kage M, Takasu O, Ogata T, et al. Investigation on portal hemodynamic—Changes of marginal zone in portal hypertension spleen. The Ministry of Health Research Project for Japan Intractable Disease Project on Aberrant Portal Hemodynamics Research Report in 2008; 2009. p. 70–3.
5. Dhiman RK, Chawla Y, Vasishta RK, et al. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature. J Gastroenterol Hepatol. 2002;17:6–16.
6. Tokushige K, Hirose S, Nishimura H, et al. Abnormal T cell activation and skewed T cell receptor V beta repertoire usage in Japanese patients with idiopathic portal hypertension. Clin Immunol Immunopathol. 1995;75:206–13.
7. Sato Y, Sawada S, Kozaka K, et al. Significance of enhanced expression of nitric oxide syntheses in splenic sinus lining cells in altered portal hemodynamics of idiopathic portal hypertension. Dig Dis Sci. 2007;52:1987–94.
8. Yamamoto K. Morphological studies of the spleen in splenomagalic liver cirrhosis comparing with the spleen in idiopathic portal hypertension (so called Banti's syndrome without liver cirrhosis). Acta Pathol Jpn. 1978;28:891–905.
9. Maesawa C, Sakuma T, Sato T, et al. Structural characteristic of splenic sinuses in idiopathic portal hypertension. Pathol Int. 1995;45:642–8.
10. Ogata T, Okuda K, Sato T, et al. Long-term outcome of splenectomy in advanced cirrhotic patients with hepatocellular carcinoma and thrombocytopenia. Kurume Med J. 2013;60:37–45.
11. Nomura Y, Kage M, Ogata T, et al. Influence of splenectomy in patients with liver cirrhosis and hypersplenism. Hepatol Res. 2014;44(10):E100–9.
12. Kercber KW, Carbonell AM, Heniford BT, et al. Laparoscopic splenectomy reverses thrombocytopenia in patients with hepatitis C cirrhosis and portal hypertension. J Gastrointest Surg. 2004;8:120–6.
13. Sugawara Y, Yamamoto J, Shimada K, et al. Splenectomy in patients with hepatocellular carcinoma and hypersplenism. J Am Coll Surg. 2000;190:446–50.
14. Hashizume M, Tomikawa M, Akahoshi T, et al. Laparoscopic splenectomy for portal hypertension. Hepatogastroenterology. 2002;49:847–52.
15. Morinaga A, Ogata T, Kage M, et al. Comparison of liver regeneration after a splenectomy and splenic artery ligation in a dimethylnitrosamine-induced cirrhotic rat model. HPB. 2010;12:22–30.
16. Kondo R, Kage M, Ogata T, et al. Therapeutic efficacy of splenectomy is attenuated by necroinflammation of the liver in patients with liver cirrhosis. J Hepatobiliary Pancreat Sci. 2015;22:217–24.
17. Cao ZX, Chen XP, Wu ZD. Changes of immune function in patients with liver cirrhosis after splenectomy combined with resection of hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int. 2003;2:562–5.
18. Levi D, Maurino E, Abecasis R, et al. Splenic hypofunction in cirrhosis is not increased risk for infections. Eur J Gastroenterol Hepatol. 1996;8:257–60.
19. Hashimoto N, Shimoda S, Kawanaka H, et al. Modulation of $CD4^+$ T cell responses following splenectomy in hepatitis C virus-related liver cirrhosis. Clin Exp Immunol. 2011;165:243–50.
20. Yoshida H, Mamada Y, Taniai N, et al. Partial splenic embolization. Hepatol Res. 2008;38:225–33.

Chapter 4
Pathology of Non-cirrhotic Liver Disease

Masayoshi Kage, Reiichirou Kondou, and Jun Akiba

Abstract The pathology of non-cirrhotic liver diseases causing portal hypertension such as extrahepatic portal obstruction, idiopathic portal hypertension, nodular regenerative hyperplasia, veno-occlusive disease, and Budd-Chiari syndrome is mainly explained.
The interrupted region of the portal circulation and hepatic blood flow pattern vary depending on disease, and several factors are combined in the mechanism of portal pressure elevation in many cases. Accordingly, the pathology varies among diseases and cases, showing diversity. Understanding the pathology of the liver and vascular system in patients with non-cirrhotic liver diseases causing portal hypertension is important to accurately clarify the diverse pathology of those diseases and useful in making a diagnosis and prognosis.

Keywords Portal hypertension · Liver pathology · Extrahepatic portal obstruction (EHO) · Idiopathic portal hypertension (IPH) · Budd-Chiari syndrome (BCS)

4.1 Introduction

The liver receives two vascular supplies: the portal vein and hepatic artery. Abnormal blood flow occurs in the liver in various liver diseases, and the blood flows of the two blood vessels interact with each other in the pathology. In this chapter, the

M. Kage (✉)
Kurume University Research Center for Innovative Cancer Therapy, Kurume, Fukuoka, Japan
e-mail: masakage@med.kurume-u.ac.jp

R. Kondou
Department of Pathology, Kurume University, School of Medicine, Kurume, Fukuoka, Japan
e-mail: kondou_reiichirou@kurume-u.ac.jp

J. Akiba
Department of Diagnostic Pathology, Kurume University Hospital, Kurume, Fukuoka, Japan
e-mail: Akiba@med.kurume-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_4

pathologies of non-cirrhotic liver diseases causing portal hypertension considered important in hepatic aberrant hemodynamics are explained. Portal pressure elevation occurs mainly due to increases in vascular resistance and portal blood flow in a region of the portal system between the portal trunk and inferior vena cava. Various diseases cause portal hypertension, and they are roughly divided into prehepatic, intrahepatic, and post-hepatic occlusions based on the obstructed region. In this chapter, representative diseases of each type, extrahepatic portal obstruction (EHO) as a prehepatic occlusion, idiopathic portal hypertension (IPH), nodular regenerative hyperplasia (NRH), and veno-occlusive disease (VOD) as intrahepatic occlusions, and Budd-Chiari syndrome (BCS) as a post-hepatic occlusion, are reviewed. Liver cirrhosis is not included in this chapter because it is explained in another chapter.

4.2 Extrahepatic Portal Obstruction (EHO)

4.2.1 Concept

In this disease, portal pressure rises due to occlusion of the extrahepatic portal vein including the hepatic hilum. The diseases of unknown and known causes of occlusion of the extrahepatic portal vein are classified as primary and secondary, respectively [1, 2]. In addition to the congenital malformation hypothesis, thrombophlebitis is considered likely as a cause of primary extrahepatic portal obstruction (EHO). The causative diseases of secondary EHO include tumors, blood disease, cholecystitis, cholangitis, and pancreatitis, showing diverse causes. In children, the incidence of thrombophlebitis and infection of the portal system is high, such as omphalitis immediately after birth, neonatal sepsis, and catheter operation-induced infection of the umbilical vein. In EHO, occlusion of the portal trunk results in cavernomatous transformation, which is hepatopetal collateral circulation formed in the hepatic hilum, being characteristic of this disease.

On imaging, development of marked hepatopetal collateral circulation consistent with closure of the extrahepatic portal vein including the hepatic hilum and cavernomatous transformation is observed on ultrasonography, CT, and MRI. The intrahepatic branch of the portal vein and hepatic vein is patent.

This hepatopetal collateral circulation is formed 1–2 weeks after portal trunk occlusion [3]. In an animal experiment using rats with EHO obstruction prepared by ligation of the portal trunk, blood flowed into the peribiliary capillary plexus communicating with the portal vein after ligation [4], the plexus gradually dilated, and cavernomatous collateral circulation formed within 1 week. This hepatopetal collateral circulation originates from a small periportal branch around the head of the pancreas, and it is considered that vascularization is involved in cavernomatous transformation.

4.2.2 Pathological Findings

4.2.2.1 Macroscopic View

Hepatopetal collateral circulation develops in the hepatic hilum area with occlusion of the extrahepatic portal vein, showing cavernomatous transformation. No change is observed on the liver surface (Fig. 4.1a, b). The portal trunk can rarely be confirmed. A large protrusion, concavity, and waving-like irregularity on the liver surface, which are observed in IPH, are present only in a few cases. Micro-cavernomatous transformation may be formed in a moderate-size intrahepatic portal vein region (Fig. 4.2a).

4.2.2.2 Histological View

In the extrahepatic portal vein, occlusion with a thrombus or tumor and severe narrowing are observed. Cavernomatous transformation is caused by outgrowth of many thin-walled vessels (Fig. 4.2b).

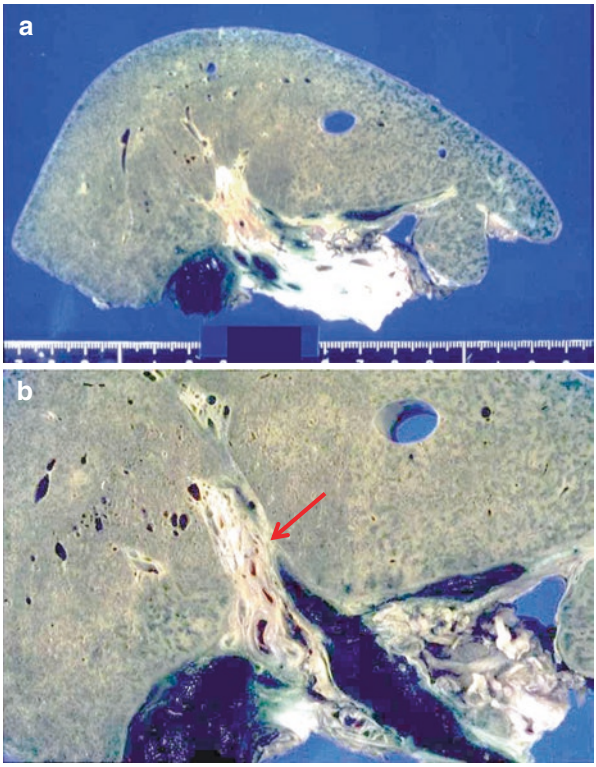


Fig. 4.1 (**a**) A cut surface of the liver of an autopsy case with extrahepatic obstruction (EHO). Cavernomatous transformation is found at the hepatic hilum. Neither cirrhotic nodule nor fibrosis is present. (**b**) Closeup view of the hilum. Many vessels are observed at the cavernomatous transformation (*arrow*)

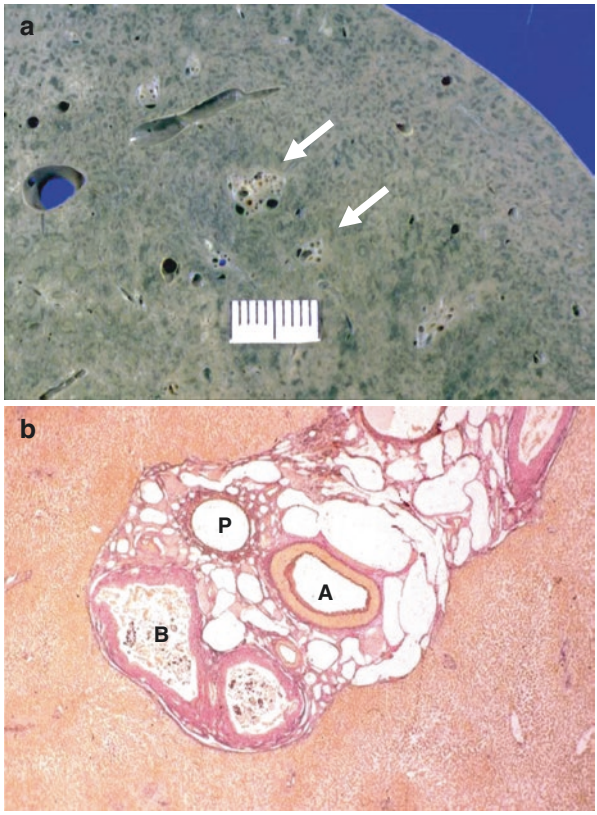


Fig. 4.2 (**a**) A cut surface of the liver of the same EHO case as in Fig. 4.1. Cavernomatous transformation is found in the medium-sized portal tract (*arrow*). (**b**) The histology of the portal tract shows the micro-cavernomatous transformation consists of many thin-walled vessels (EVG stain). *A* hepatic artery, *P* portal vein, *B* bile duct

No finding of liver cirrhosis is observed. Normally, hepatic lobule construction is retained, and the intrahepatic branch of the portal vein is patent, but collapse or narrowing of the portal branch similar to that in IPH may be observed in some cases of EHO.

Some cases show no marked histological change.

4.3 Idiopathic Portal Hypertension (IPH)

4.3.1 Concept

IPH represents diseases in which splenomegaly, anemia, and portal pressure elevation occur but no causative disease, such as liver cirrhosis, occlusion of extrahepatic portal vein/hepatic vein, blood disease, parasitic disease, granulomatous liver disease, or congenital hepatic fibrosis, can be demonstrated [5–7].

Regarding geographical prevalence of IPH, it was previously high in India and developing countries [5], but non-cirrhotic IPH patients have recently decreased worldwide, probably due to improvement of social and environmental conditions.

The main clinical symptoms of this disease are splenomegaly, anemia, portal hypertension, abdominal wall varicosis, and edema. Hematemesis/melena and anemia are observed in about 40% of cases. Esophageal/gastric varix, portal hypertension-associated gastroenteropathy, ectopic varices, and ascites develop in association with portal hypertension, and symptoms of hemorrhagic tendency, liver dysfunction, and hepatic encephalopathy appear [6, 7]. Generally, this disease does not progress to liver cirrhosis; however hepatocellular carcinoma may complicate although it is very rare [5, 7]. Hepatic atrophy may progress to liver failure.

For the cause of this disease, hepatogenic theory, such as intrahepatic peripheral thrombus, splenogeic theory, and abnormal autoimmunity theory have been proposed [5–8].

The hemodynamics of this disease is understood as elevation of portal blood flow resistance by occlusion of the presinusoidal intrahepatic portal vein, and collapse and narrowing of the peripheral branch of the portal vein are considered histopathological findings corresponding to this.

Since this disease frequently develops in middle-aged women, and autoimmune disease is likely to concomitantly develop, abnormal autoimmunity is considered the cause [6]. Regarding the pathological findings of IPH, Nakanuma et al. pointed out that small portal veins and skin findings are similar between patients with scleroderma and those with IPH [9]. They reported that transforming growth factor-β [10] and connective tissue growth factor which are fibrosis-related, and vascular endothelial growth factors, increase in the serum, skin, and the portal vein, attracting attention as a cause of this disease.

4.3.2 Pathological Findings

4.3.2.1 Macroscopic View of the Liver

The liver surface shows waving-like irregularity and small folds in many cases. Atrophy is not noticeable in early-stage IPH, but when the period with illness becomes prolonged, the liver weight decreases, and the overall liver morphology becomes deformed, or the right or left lobe becomes extremely small at the advanced stage [5, 8, 9] (Fig. 4.3). The main branch of the intrahepatic portal vein is thickened and dilated. The intermediate-sized portal vein regions (regions receiving the fifth to sixth branches of the portal vein) fibrously expand and get close to each other or to the liver capsule, and the branch of the portal vein is narrowed. In the peripheral portal vein regions, narrowing of the branches is noticeable, and the portal venous

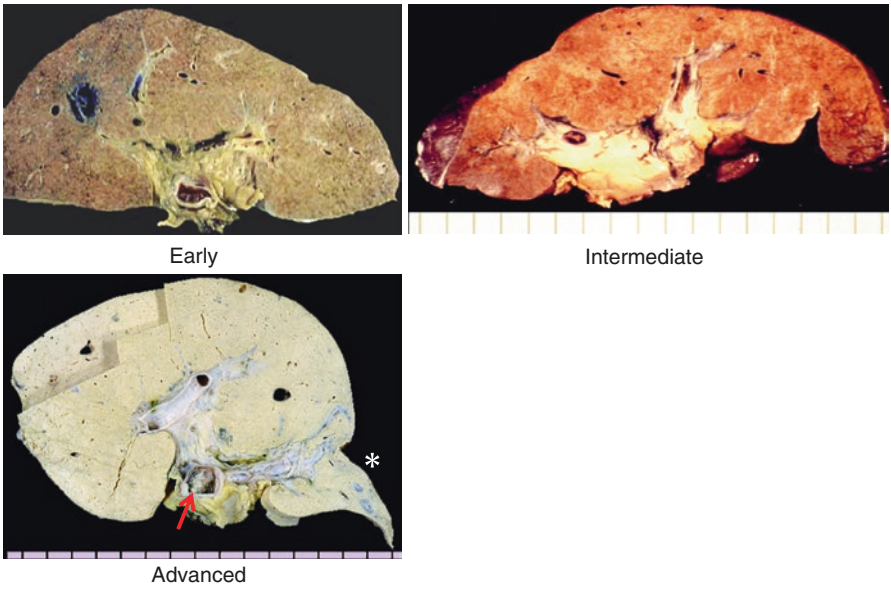


Fig. 4.3 A cut surface of the liver of autopsy cases with idiopathic portal hypertension (IPH) in three stages. Early stage: The liver is mildly atrophic. No cirrhotic nodule is present. Intermediate stage: The atrophy is more pronounced. The shape of the liver is distorted due to irregular extinction of the hepatic parenchyma in the subcapsular region. Advanced stage: The liver is markedly atrophic. A thrombus is observed in the portal vein at the hilum (*arrow*). Note the deformed and shrunken left hepatic lobe (*asterisk*)

regions get close to each other, but depopulation is observed depending on the region. Hyperplastic nodules may be mainly present in the hepatic hilum and around intermediate-size portal vein regions in many cases.

4.3.2.2 Histological View of the Liver

The portal tracts show round fibrous expansion. Extension of irregular fibers into liver parenchyma may occasionally be observed. The wall is markedly thickened, and the lumen is narrowed in the portal branch in many cases. Intermediate-sized portal branches may be accompanied by hyperplasia of smooth muscle layer of the media of the portal vein. In the most peripheral portal tract, narrowing, collapse, and loss of the portal vein branch are observed [5, 8, 9, 11] (Fig. 4.4).

Abnormally dilated vessels with a thin wall (abnormal aberrant vessel) are frequently observed in contact with the portal tract [8, 11] (Fig. 4.5). Generally, inflammatory cell infiltration is not observed.

Hyperplastic nodules are formed by hyperplasia of hepatocytes with no atypia, and lesions of nodular regenerative hyperplasia NRH described in the following Sect. 4.4 and focal nodular hyperplasia (FNH)-like lesions may be present in the histological view.

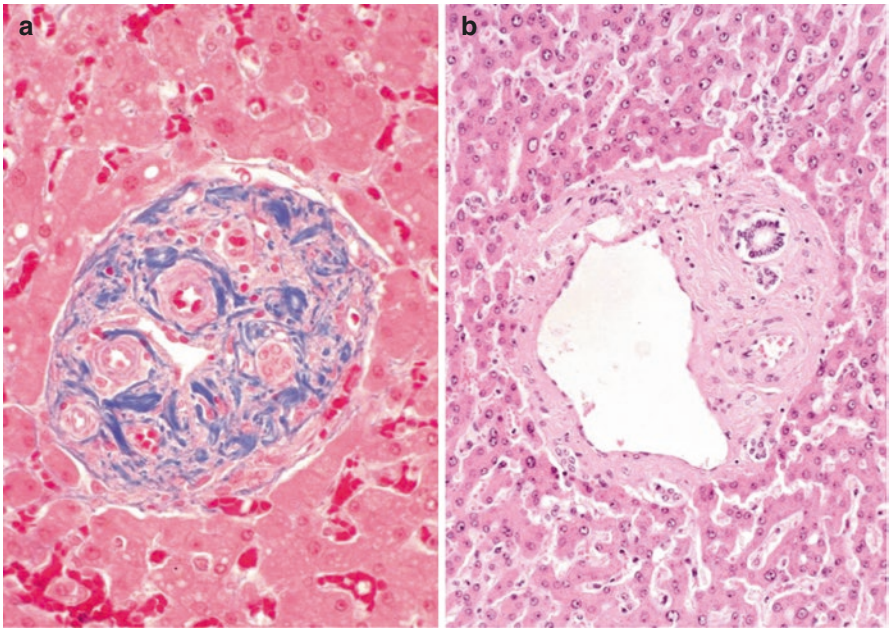


Fig. 4.4 (**a**) A peripheral portal tract shows occlusion of the portal vein (Azan stain). The lumen of the portal vein is not recognized. (**b**) Normal portal tract (H&E stain). The portal vein is patent

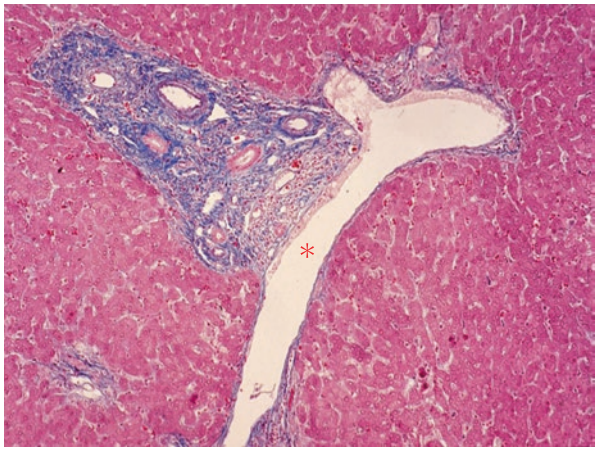


Fig. 4.5 There is a thin-walled vessel, an aberrant pathway (*asterisk*), adjacent to a peripheral portal tract (Azan stain)

4.4 Nodular Regenerative Hyperplasia (NRH)

4.4.1 Concept

NRH is a pathological concept proposed by Steiner in 1959 [12]. Its characteristic is small nodule formation comprised of diffuse hyperplastic hepatocytes, and many

nodules are smaller than hepatic lobules. The difference of NRH from liver cirrhosis is the absence of fibrous septum surrounding nodules observed in liver cirrhosis. These lesions have been expressed as various terms, such as miliary hepatocellular adenomatosis, nodular transformation of the liver, nodular noncirrhotic liver, and non-cirrhotic nodulation [13, 14].

NRH is mainly observed in adults, and it is rare in children. Regarding sex difference, the incidence is slightly higher in females. Normally, NRH develops concomitantly with system disease [12–16]. Steiner [12] found NRH in a congestive liver associated with non-compensatory heart failure, but it is also observed in various diseases. The frequency is high in autoimmune diseases, such as Felty syndrome, rheumatoid arthritis, systemic lupus erythematosus, CREST syndrome, and polyarteritis nodosa, but it also develops with diverse underlying diseases, such as polycythemia vera [16], lymphoproliferative disease, blood disease, congestive heart failure, diabetes, and primary biliarycholangitis. Clinically, it is asymptomatic. In cases in which NRH was incidentally discovered at autopsy, rupture of esophageal varices with portal pressure elevation or hypersplenism was observed in some cases. No or mild abnormality is observed in the liver function on biochemistry.

4.4.2 Pathological Findings of the Liver

The disease concept of NRH is based on the pathological morphology of the liver, and it is simple and clear. However, the pathological morphology of the liver previously reported as NRH has been found diverse, and nodule formation is not necessarily diffuse, or the nodule size is heterogeneous in some cases, i.e., cases not meeting Steiner's criteria [12] are also regarded as NRH.

4.4.2.1 Macroscopic Findings

The typical macroscopic features of NRH are a microgranular liver surface and the presence of diffuse-white or yellowish-white nodules with a homogenous size of 3 mm in the cross-section surface throughout the liver with an appearance similar to that of liver cirrhosis (Fig. 4.6a). When it is carefully observed, a peripheral portal vein region appearing as a dot is present in the center of the nodules. Nodules have a lobule-unit size in typical cases but may reach several centimeters in some cases (Fig. 4.6b).

4.4.2.2 Histological Findings

The hepatic lobular architecture is recognizable. Nodules are mainly formed in peripheral portal tracts, and the nodule size is relatively homogeneous and small, being smaller than the original hepatic lobule size, i.e., recognized as sublobular nodules (Fig. 4.6c). Hepatic cords of hepatocytes forming nodules are two to three

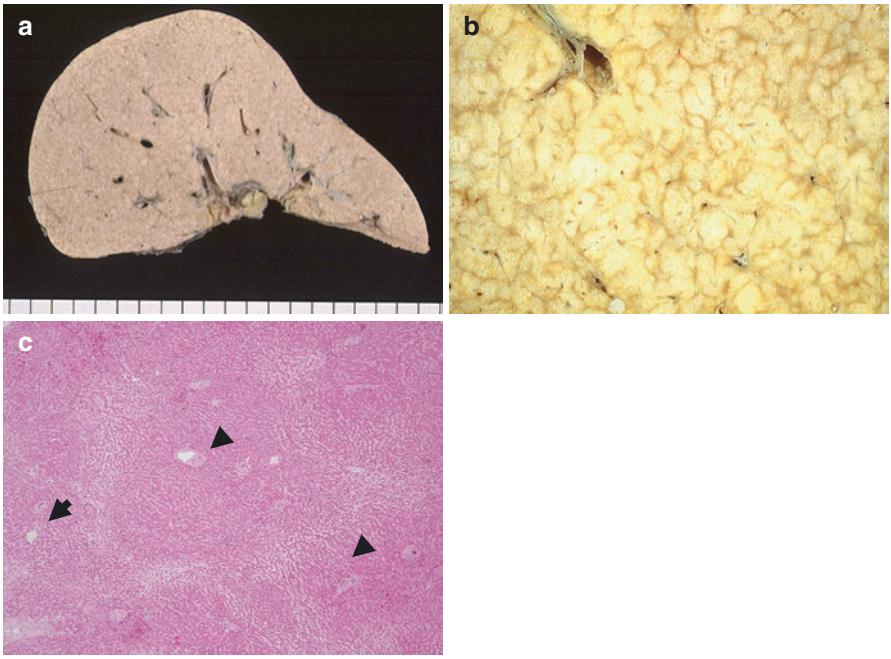


Fig. 4.6 Liver pathology of nodular regenerative hyperplasia (NRH). (**a**) The cut surface of the liver of an autopsy case with NRH, showing diffuse nodular formation. (**b**) Closeup view of (**a**), showing uniform micro-nodules. (**c**) The histology of the nodules. The nodules are composed of hyperplastic hepatocytes and have peripheral portal tracts (*arrow head*) in the center of nodules (H&E stain)

layers thick. No fibrous septum is present between nodules, being different from that in liver cirrhosis. Fibrosis is absent or mild in the portal tracts.

4.5 Veno-Occlusive Disease (VOD)

4.5.1 Concept

In VOD, severe congestion of the liver is caused by non-thrombotic occlusion or stenosis of the hepatic central vein or sublobular vein [17]. However, it was recently considered that the main pathology of VOD is impairment of sinusoidal endothelial cells, subsequent sinusoidal fibrosis and microcirculatory disorder, and resulting impairment of hepatocytes in zones 2–3, and a name, sinusoidal obstructive syndrome (SOS), has been proposed [18].

The causes of VOD are diverse, such as allogeneic bone marrow transplantation, plant alkaloid poisoning, and administration of immunosuppressors and anticancer agents, and the incidence varies depending on the cause [17–19].

Clinically, hepatomegaly, ascites, jaundice, and weight gain are observed, and some cases develop liver failure. The disease course is chronic, and some cases progress to congestive liver cirrhosis. Serologically, endothelial cell markers, such as hyaluronic acid and inflammatory cell markers, such as tumor necrosis factor-alpha (TNF-α), increase in conjunction with increases in ALT, AST, and bilirubin [17–19].

4.5.2 Pathological Morphology of the Liver

4.5.2.1 Macroscopic Findings

The cut surface of the liver with VOD is characteristic where expansion of congestion is irregular and distributed in a geographic pattern. This liver congestion is also observed in right-sided heart failure and BCS, but congestion regularly appears in the centrilobular zone (zone 3) in these diseases, being different from the macroscopic view of VOD.

4.5.2.2 Histological Findings

The lumen of the sublobular or central vein occlusion [17, 18] is associated with congestion and hepatic necrosis (Fig. 4.7a, b). The sinusoid is congested, extravascular leakage of red blood cells into Disse's space occurs, and hepatocytes necrotize. Sinusoidal occlusion results in ischemia, internal sinusoidal pressure elevation, and fragmentation of hepatic cords. Fragmented hepatocytes further promote circulatory disorder, causing reflux into the portal vein and embolism of the damaged central vein. Occlusion of the central vein is not observed in some cases of VOD (Fig. 4.7a). It has been reported that the occlusion was observed in 55% of

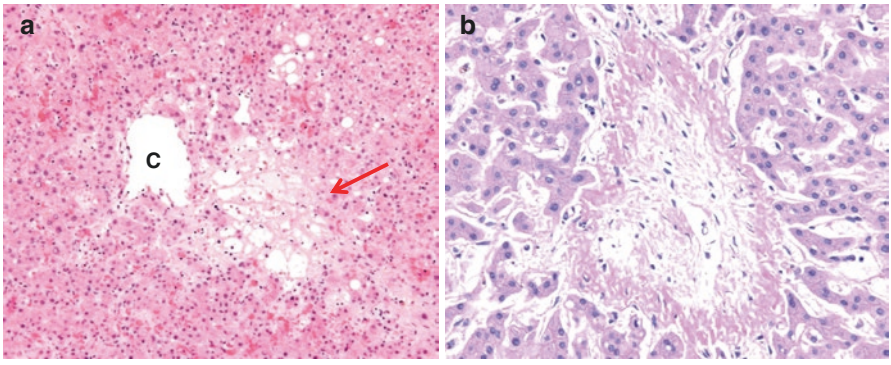


Fig. 4.7 Liver histology of veno-occlusive disease. (**a**) An indistinct area of focal hepatocyte necrosis (*arrow*) near the patent central vein (**c**). (**b**) A completely occluded sublobular hepatic vein

mild-moderate VOD cases and 75% of severe VOD cases among autopsied cases clinically diagnosed as VOD [17]. As described above, occlusion of the central vein is not a universal feature of VOD.

4.6 Budd-Chiari Syndrome (BCS)

4.6.1 Concept

BCS is defined as a disease developing symptoms of occlusion or stenosis of the three main trunks of the hepatic vein or hepatic inferior vena cava [20].

BCS is divided into cases with a clear cause such as blood coagulation disorder including polycythemia vera and protein S deficiency, thrombus formation in the hepatic vein or inferior vena cava induced by oral contraceptive ingestion, and tumor embolism with hepatocellular carcinoma and kidney cancer, and idiopathic cases of unknown cause. In Western countries, the cause of BCS is clear as occlusion of a thick hepatic vein in most cases [21], whereas most cases are idiopathic in Japan [22] and developing countries such as South Africa [23] and Nepal [24], where the hepatic inferior vena cava is occluded in many cases.

Regarding clinical symptoms, some cases rapidly develop symptoms such as fever, abdominal pain, and ascites, while others become chronic with unclear onset time of symptoms [24]. When the course becomes chronic, congestive liver progresses to congestive liver fibrosis and then liver cirrhosis. Important concomitant diseases are hepatocellular carcinoma and portal hypertension. In portal hypertension, esophageal varices, splenomegaly, and ascites develop.

4.6.2 Cause and Pathological Morphology of Obstruction of the Inferior Vena Cava and Hepatic Vein

In idiopathic BCS described above, the inferior vena cava in the hepatic region is occluded in many cases. This inferior vena cava occlusion was conventionally called membranous obstruction of the inferior vena cava (MOVC) based on its shape, but the occluded region and its morphology are diverse, the shape of obstruction is far different from thin "membrane" in some cases, and occlusion extends to a 2–3 cm in length or is funnel-shaped in other cases [22, 25]. Thus, the morphology of MOVC is diverse, and the body of the "membrane" was organized thrombus in our autopsy cases on pathological examination [25] (Fig. 4.8). Not all organized thrombi were old, but various old and new thrombi were coexisting, and recanalization of thrombus, calcification, and hemosiderin deposition were observed. It is likely that MOVC is derived from acquired thrombus formation in addition to congenital malformation, and Shrestha et al. reported a study supporting this from Nepal [24].

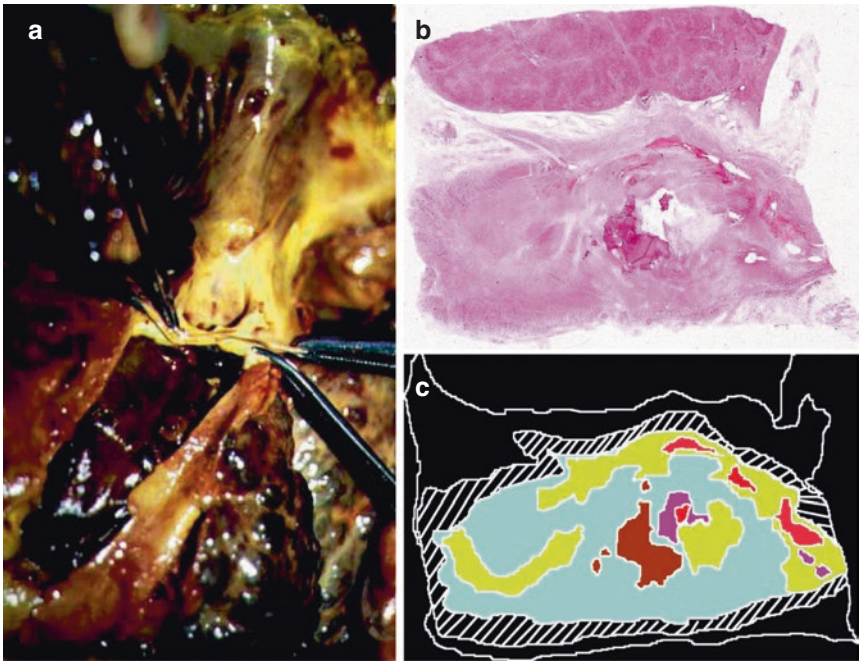


Fig. 4.8 (**a**) Gross appearance of membranous obstruction of the inferior vena cava (IVC) at the hepatic portion in an autopsy case with Budd-Chiari syndrome. The membrane, 2 mm in thickness, is picked by the forceps. Asterisk: fresh thrombus in the IVC. (**b**) The histology of the membrane at the IVC. (**c**) Schema of the histology of the membrane in (**b**). The membrane of the IVC is composed of thrombus in the diverse process of the organization including calcification and recanalization

The characteristics of the epidemiology and clinical view of MOVC in Nepal are background factors, such as malnutrition and alcoholism, being of low socioeconomic status in regions with poor hygiene conditions, and MOVC frequently develops with bacterial infection. Causative bacteria, such as *Escherichia coli* and *Staphylococcus*, were confirmed by blood culture in about 1/3 of cases. It is assumed that infection causes thrombophlebitis of the hepatic inferior vena cava and forms MOVC as the outcome of organized thrombus.

4.6.3 Pathological Morphology of the Liver

4.6.3.1 Macroscopic View

Acute or chronic congestive hepatic lesions develop. The grade and expansion of congestion or progression of fibrosis vary among patients. In acute cases, congestive hepatomegaly develops. Long-term cases progress to congestive hepatic fibrosis and then congestive liver cirrhosis.

4.6.3.2 Histological View

In acute cases, sinusoidal congestive dilation and necrosis of hepatocytes are observed in the central zone of hepatic lobules, and thrombotic obstruction of branches of the hepatic vein is often observed in a wide range of acute fetal cases. In chronic cases, fibrosis advances from the central zone of hepatic lobules and results in reversed lobulation due to bridging fibrosis between the central veins (Fig. 4.9). Reversal of the hepatic lobular structure represents a state in which the portal vein region is present in the center of the hepatocyte population surrounded by the fibrous band. Obstruction of the hepatic vein branch with thrombus is often observed, but the grade and expansion vary among cases.

In BCS, benign hepatic hyperplastic nodules and hepatocellular carcinoma may be observed [21–23, 25]. The association of the frequency and cause of hyperplastic nodules with carcinogenesis in the liver has not been sufficiently clarified. Nodular lesions similar to FNH and NRH are also observed even in early congestive liver. Regarding the cause of hyperplastic nodules, FNH-like nodules or NRH are assumed to be formed due to abnormal intrahepatic circulation based on its histological findings [21].

In idiopathic BCS, concomitant hepatocellular carcinoma frequently develops. According to Kew et al. [23] from South Africa, the frequency of MOVC in all liver

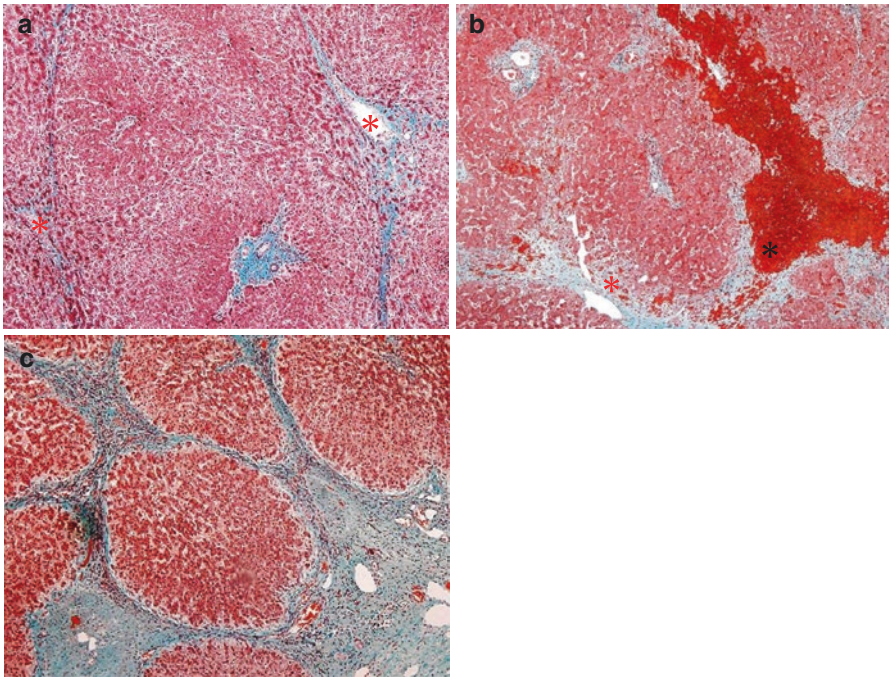


Fig. 4.9 Liver histology of chronic passive congestion in Budd-Chiari syndrome (Azan stain). (**a**) Mild fibrosis starts from the central zone (*asterisk*). (**b**) Reversed lobulation: Bridging fibrosis between the central zones (asterisk) to form a nodular change. (**c**) Congestive liver cirrhosis

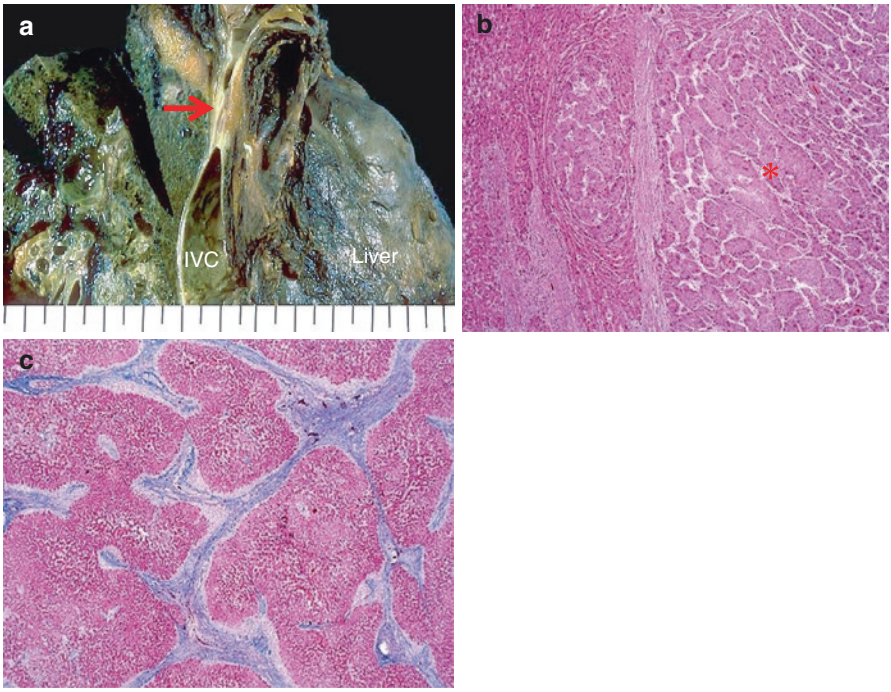


Fig. 4.10 (**a**) Gross appearance of an autopsy case with Budd-Chiari syndrome with obstruction of the IVC (*arrow*). (**b**) The liver histology shows complication of hepatocellular carcinoma (*asterisk*). (**c**) Non-cancerous liver shows chronic congestive fibrosis (Azan stain)

cancer cases was 3.7% (6/166) in black liver cancer patients. They organized references concerning MOVC in South Africa and observed that the frequency of liver cancer was high (43.5%; 57 of 131 MOVC cases including their patients). In Japan, Nakamura et al. [26] reported that the frequency of concomitant liver cancer was high (42%). Thus, BCS is as high a risk factor for liver cancer as viral hepatitis.

The non-cancer region appears like liver cirrhosis in most BCS patients with concomitant liver cancer, but there is also a risk of developing liver cancer from the state of hepatic fibrosis (Fig. 4.10).

The involvement of hepatitis virus in carcinogenesis in the liver with MOVC has not been emphasized in any previous report.

References

1. Sarin SK, Sollano JD, Chawla YK, Amarapurkar D, Hamid S, Hashizume M, Jafri W, Kumar A, Kudo M, Lesmana LA, Sharma BC, Shiba SG, de Silva HJ, Members of the APASL Working Party on Portal Hypertension. Consensus on extra-hepatic portal vein obstruction. Liver Int. 2006;26:512–9.
2. Kunio O, Aoki H. Extrahepatic portal vein obstruction. In: Okuda K, Benhamou JP, editors. Portal hypertension. Tokyo: Springer; 1991. p. 365–79.

3. Ohnishi K, Okuda K, Ohtsuki T, et al. Formation of hilar collaterals or cavernous transformation after portal vein obstruction by hepatocellular carcinoma. Observations in ten patients. Gastroenterology. 1984;87:1150–3.
4. Cho KJ, Lunderquist A. The peribiliary vascular plexus: the microvascular architecture of the bile duct in the rabbit and in clinical cases. Radiology. 1983;147:357–69.
5. Okuda K, Nakashima T, Okudaira K, et al. Liver pathology of idiopathic portal hypertension. Comparison with non-cirrhotic portal fibrosis of India. Liver. 1982;2:176–92.
6. Dhiman RK, Chawla Y, Vasishta RK, et al. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature. J Gastroenterol Hepatol. 2002;17:6–16.
7. Siramolpiwat S, et al. Idiopathic portal hypertension: natural history and long-term outcome. Hepatology. 2014;59:2276–85.
8. Okudaira M, Ohbu M, Okuda K. Idiopathic portal hypertension and its pathology. Semin Liver Dis. 2002;22:59–71.
9. Nakanuma Y, Sato Y, Kiktao A. Pathology and pathogenesis of portal venopathy in idiopathic portal hypertension: hints from systemic sclerosis. Hepatol Res. 2009;39(10):1023–31. https://doi.org/10.1111/j.1872-034X.2009.00555.x.
10. Kitao A, Sato Y, Sawada-Kitamura S, et al. Endothelial to mesenchymal transition via transforming growth factor-beta1/Smad activation is associated with portal venous stenosis in idiopathic portal hypertension. Am J Pathol. 2009;175(2):616–26. https://doi.org/10.2353/ajpath.2009.081061.
11. Ohbu M, Okudaira M, Watanabe K, et al. Histopathological study of intrahepatic aberrant vessels in cases of noncirrhotic portal hypertension. Acta Hepatol. 1994;20:302–8.
12. Steiner PE. Nodular regenerative hyperplasia of the liver. Am J Pathol. 1959;35:943–53.
13. Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2500 autopsies and a new classification of benign hepatocellular nodules. Hepatology. 1990;11:787–97.
14. Stromeyer FW, Ishak KG. Nodular transformation (nodular regenerative hyperplasia) of the liver-a clinico-pathologic study of 30 cases. Hum Pathol. 1981;12:60–71.
15. Nakanuma Y. Nodular regenerative hyperplasia of the liver: retrospective survey in autopsy series. J Clin Gastroenterol. 1990;12:460–5.
16. Wanless IR, Goldwin TA, Allen F, et al. Nodular regenerative hyperplasia of hematologic disorders: a possible response to obliterative portal venopathy-a morphometric study of nine cases with hypothesis on the pathogenesis. Medicine. 1980;59:367–79.
17. Shulman HM, Fisher LB, Schoch HG, et al. Veno-occlusive disease of the liver after marrow transplantation: histological correlates of clinical signs and symptoms. Hepatology. 1994;19:1171–81.
18. DeLeve LD, Shulman HM, McDonald GB. Characterization of a reproducible rat model of hepatic veno-occlusive disease. Hepatology. 1999;29:1779–91.
19. McDonald GB, Sharma P, Matthews D, et al. Venoocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology. 1984;4:116–22.
20. Valla DC. The diagnosis and management of the Budd-Chiari syndrome: consensus and controversies. Hepatology. 2003;38:793–803.
21. Tanaka M, Wanless I. Pathology of the liver in Budd-Chiarisyndrome: portal vein thrombosis and the histogenesis of veno-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodule. Hepatology. 1998;27:488–96.
22. Okuda K. Membranous obstruction of the hepatic portion of the inferior vena cava. Etiology and relation to hepatocellular carcinoma. Gastroenterology. 1982;82:376–9.
23. Kew MC, McKnight A, Hodkinson J, et al. The role of membranous obstruction of the inferior vena cava in the etiology of hepatocellular carcinoma in Southern African blacks. Hepatology. 1989;9:121–5.

24. Shrestha SM, Okuda K, Uchida T, et al. Endemicity and clinical picture of liver disease due to obstruction of the hepatic portion of the inferior vena cava in Nepal. J Gastroenterol Hepatol. 1996;11:170–9.
25. Kage M, Arakawa M, Kojiro M, et al. Histopathology of membranous obstruction of the inferior vena cava in the Budd-Chiari syndrome. Gastroenterology. 1992;102:2081–90.
26. Nakamura T, Nakamura S, Aikawa T, et al. Obstruction of the inferior vena cava in the hepatic portion and the hepatic veins. Angiology. 1968;19:479–98.

Part II
Clinical Pathophysiology and Diagnosis of Portal Hypertension

Chapter 5
Mechanism and Pathophysiology of Portal Hypertension

Atsushi Toyonaga

Abstract This chapter discusses the developmental and pathophysiological mechanisms of portal hypertension and the consequent formation of esophagogastric varices. Anatomical and pathophysiological findings regarding the diagnosis and treatment of varices can provide useful information for clinical practice. In addition, hemodynamic changes caused by treatment are also described. Endoscopic treatment is well indicated for esophagogastric varices, irrespective of urgent, elective, or prophylactic purposes. As an endoscopic treatment-resistant condition, a pipeline stem varix of the esophagus is presented.

Among gastric varices, acutely bleeding large isolated gastric fundal varices (IGFVs) that do not communicate with esophageal varices are resistant to endoscopic treatment and require the use of *n*-butyl-2-cyanoacrylate (tissue adhesive glue) injection for hemostasis. Patients with large IGFVs often have portosystemic shunts, mainly splenorenal (S-R) shunts, and are prone to recurrent hepatic encephalopathy.

Balloon-occluded retrograde transvenous obliteration (B-RTO), a procedure developed in Japan, can totally eradicate large IGFVs with S-R shunts. With major shunt obliteration achieved, B-RTO is also markedly effective against shunt encephalopathy. Portosystemic shunt syndrome (portosystemic shuntopathy), which has been defined based on accumulated B-RTO case data, is also described herein.

Keywords Esophagogastric varices · Balloon-occluded retrograde transvenous obliteration (B-RTO) · Portosystemic shunt syndrome (portosystemic shuntopathy) Pipeline stem varix · Point of no return

A. Toyonaga
Kurume University, School of Medicine, Kurume, Fukuoka, Japan

Yasumoto Hospital, Kurume, Fukuoka, Japan
e-mail: atsushi-toyonaga@w3.dion.ne.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_5

5.1 Portal Hypertension and Collaterals

In portal hypertension, esophagogastric varices are formed at high rates and are often fatal if bleeding, rendering them a critical complication that determines prognosis. While the normal portal pressure is 100–150 mm H_2O (1 mm Hg = 13.6 mm H_2O), in cases of portal hypertension, values remain elevated at ≥200 mm H_2O. Wedged hepatic venous pressure, which does not involve a direct puncture of the portal vein, is a common alternative to portal pressure. Increased vascular resistance anywhere in the pathway from the intrahepatic portal venules via the sinusoids (terminal capillary beds) through the hepatic veins or increased blood inflow from the intraabdominal viscera, except the retroperitoneal kidneys, causes portal venous engorgement, elevating portal blood pressure (i.e., portal hypertension). As a result, as the portal vein does not have a backflow prevention valve, backflow occurs in portal system tributaries, leading to formation of portosystemic venous collaterals (Fig. 5.1), part of which presents as esophagogastric varices. The development of collaterals is a physiological adaptive phenomenon. However, extensive portal steal increases the risk of hepatic dysfunction and death from variceal hemorrhage.

5.2 Mechanism of the Onset of Portal Hypertension

Portal pressure (P) is defined based on portal blood flow volume (V) and intrahepatic vascular resistance to V (R), expressed as $P = V \times R$ (Ohm's law). The portal blood flow volume is regulated by visceral blood flow volume. Neurohumoral factor-based homeostasis, which compensates for any change in portal blood flow, maintains portal pressure within the normal range by regulating portal vascular resistance. Portal hypertension can be deemed as a consequence of the failure of a compensatory mechanism to address a pathological increase in portal vascular resistance or portal blood flow volume.

5.2.1 Increased Portal Vascular Resistance

Besides the regenerated nodules in the cirrhotic liver, which are believed to be a contributory factor to generating portal vascular resistance [1], increased collagen deposition in the space of Disse in the hepatic microstructure diminishes the sinusoidal diameter and thereby elevates intrahepatic vascular pressure. The amount of collagen deposit in the space of Disse correlates with sinusoidal pressure (indication of portal pressure) [2]. This concept is supported by the fact that portal pressure is increased in fatty liver free of regenerated nodules and in alcoholic hepatitis. Some researchers suspect that hepatocyte hypertrophy due to accumulated fat or water

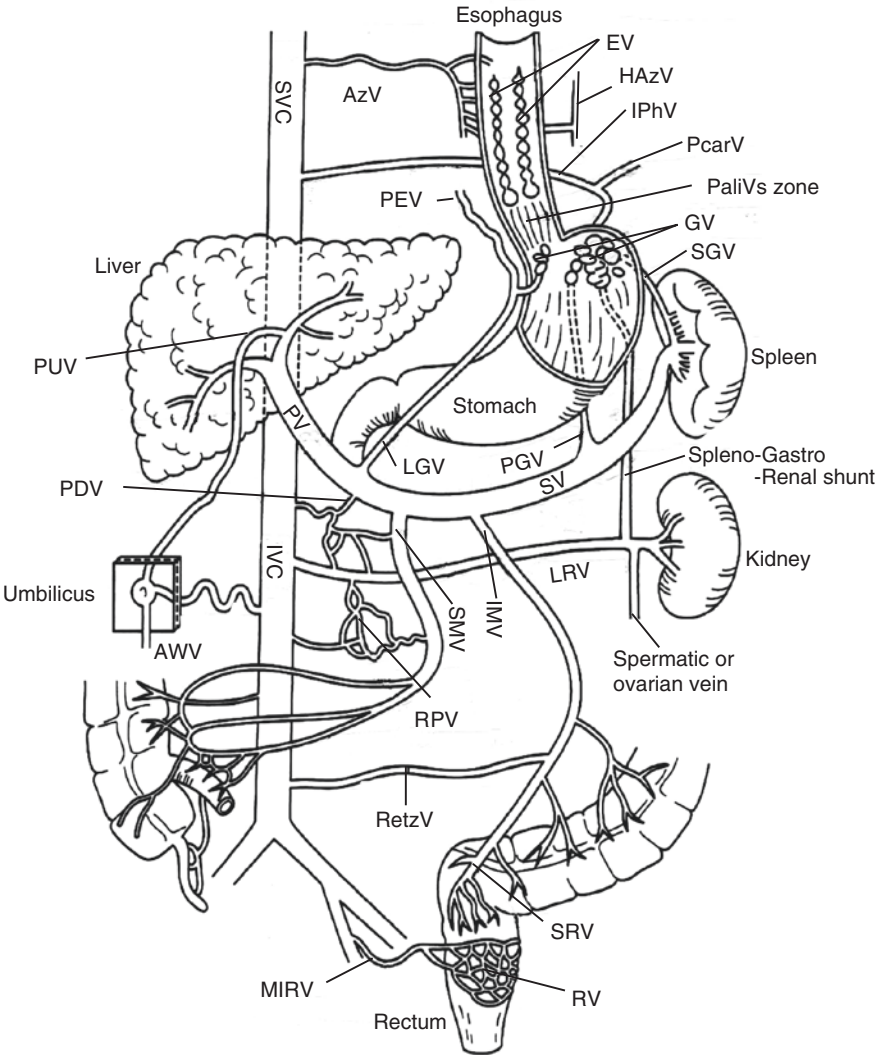


Fig. 5.1 Collaterals in portal hypertension *by Toyonaga*. *EV* esophageal varices, *AzV* azygos vein, *SVC* superior vena cava, *HAzV* hemiazygos vein, *IPhV* inferior phrenic vein, *PcarV* pericardiac vein, *PaliVs zone* palisading veins zone, *PEV* paraesophageal vein, *GV* gastric varices, *SGV* short gastric vein, *PGV* posterior gastric vein, *LGV* left gastric vein, *PV* portal vein, *SV* splenic vein, *PUV* paraumbilical vein, *IVC* inferior vena cava, *AWV* abdominal wall vein, *PDV* pancreatico-duodenal vein, *SMV* superior mesenteric vein, *IMV* inferior mesenteric vein, *LRV* left renal vein, *RPV* retroperitoneal paravertebral vein, *RetzV* Retzius's vein, *SRV* superior rectal vein, *MIRV* middle and inferior rectal veins, *RV* rectal varices

may lead to higher portal pressure. This hypothesis is backed by a clinical observation that portal pressure is dependent on alcohol intake or withdrawal. In particular, portal hypertension progression results from interactions between morphological changes in hepatocyte and collagen deposition in the space of Disse. In addition, in the hepatic vascular system, adrenergic receptors are present and under complicated control by neurohumoral factors [3]. Moreover, contractile myofibroblasts, known to reside in perisinusoidal locations and fibrotic septa, contribute to increased hepatic vascular pressure [3, 4]. As mentioned earlier, a combination of morphological and functional changes in the intrahepatic vascular bed elevates portal vascular resistance, resulting in portal hypertension (backward-flow mechanism).

5.2.2 Increased Portal Blood Flow Volume

Elevated portal pressure as a result of higher intrahepatic vascular resistance leads to the development of collaterals of lower vascular resistance, but portal hypertension remains. This is contradictory because, in the presence of collaterals, overall vascular resistance in the portal system and, subsequently, portal pressure should decrease according to Ohm's law. Here, the presence of hyperdynamic circulation in portal hypertension should be clearly understood [5, 6]. The hyperdynamic circulation is characterized by peripheral vascular dilatation (decreased peripheral vascular resistance) and cardiac output increase (collateral development, plasma volume increase, and arteriovenous shunting in the microcirculation).

As hepatic elimination capacity decreases and/or portosystemic shunts (PSSs) are formed, plasma levels of glucagon and other vasodilators (hepatic vasodilatory substances, vasoactive polypeptides, prostaglandins, endotoxins, endothelial cell-independent factors, and nitric oxide) increase. This results in visceral and peripheral vascular dilatation and decreased vascular resistance. In addition, vascular sensitivity to a vasoconstrictor catecholamine diminishes [3, 7]. Lower effective circulating plasma volume resulting from visceral vascular dilatation stimulates the renin-angiotensin-aldosterone system, causing sodium/water retention and plasma volume increase [5, 8]. Such hyperdynamic circulation enhances splanchnic blood flow and retains portal hypertension (forward-flow mechanism).

As described earlier, two factors, the forward- and backward-flow mechanisms, are involved in the onset and maintenance of portal hypertension (Fig. 5.2) [6].

5.3 Classification of Portal Hypertension According to the Location of the Cause

The causes are divided into prehepatic, intrahepatic, and posthepatic locations. A typical prehepatic portal hypertension is an extrahepatic portal obstruction. Intrahepatic portal hypertension is subdivided according to the site of increased

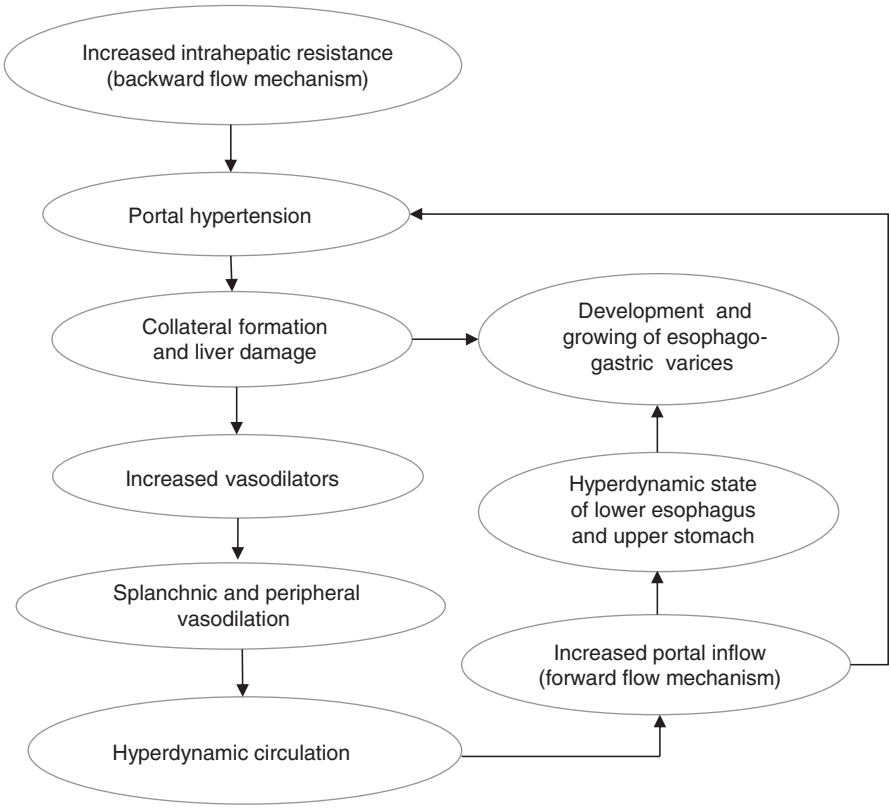


Fig. 5.2 Development and maintenance of portal hypertension with esophagogastric varices

vascular resistance, as presinusoidal (e.g., idiopathic portal hypertension, schistosomiasis japonica, and congenital hepatic fibrosis), sinusoidal (fatty liver and liver cirrhosis), or postsinusoidal types (e.g., veno-occlusive disease). The main causes of posthepatic portal hypertension include hepatic vein obstruction (Budd-Chiari syndrome) and inferior vena caval obstruction (Table 5.1). In Japan, the most common (about 80–90%) cause of portal hypertension is liver cirrhosis.

5.4 Mechanisms of the Development of Esophagogastric Varices

In addition to increased intrahepatic vascular resistance and portal blood inflow volume, which result in elevated portal pressure and backward blood flow in the left gastric vein and in the short or posterior gastric veins, a local hyperdynamic

Table 5.1 Classification of portal hypertension according to the location of cause

Classification of portal hypertension	Underlying diseases	Characteristics and clinical examinations
Prehepatic PH	Extrahepatic portal obstruction	Cavernous formation at hepatic hilum
	Portal thrombosis	US, CT, Portography
Intrahepatic PH (site of vascular resistance)	Idiopathic PH (presinusoidal)	Normal or mildly elevated HVPG Peripheral hepatic vein-to-vein Anastomoses
	Schistosomiasis(presinusoidal)	Tortoiseshell pattern on hepatic US
	Liver cirrhosis(sinusoidal)	HVPG = PVP
	Viral liver cirrhosis	Viral marker
	Alcoholic liver cirrhosis	History
	Autoimmune hepatitis	Hyper γ-globurinemia, positive ANAB
	Primary biliary cirrhosis	Positive AMAB
	Veno-occlusive disease(postsinusoidal)	Marked decrease of hepatic inflow
Posthepatic PH	Budd-Chiari syndrome	Stenosis or obstruction of hepatic vein, and association of IVC obstruction
	IVC hepatic portion obstruction	Congestion of IVC network and collaterals

PH portal hypertension, *IVC* inferior vena cava, *HVPG* hepatic venous pressure gradient, *PVP* portal vein pressure, *ANAB* anti-nuclear antibody, *AMAB* anti-mitochondrial antibody, *US* ultrasonography, *CT* computed tomography

state in the upper gastric region plays a role in the onset and development of varices [9]. In cases of portal hypertension, peripheral shunting of the left gastric arterial blood into the left gastric vein may occur, triggering the formation of varices. In the left gastric vein, to-and-fro, hepatopetal, and hepatofugal blood flow are observed, indicating the presence of left gastric arterial inflow in addition to portal backflow [10].

Anatomically, at the lower end of the esophagus, a specific vascular structure is observed that extends cephalad for about 3 cm from the esophagogastric mucosal junction (squamocolumnar junction), termed *palisading veins*, where the portal circulation meets the systemic circulation [11–14] (cf. Figs. 5.1 and 5.6). This zone comprises numerous veins, mainly about 80% of those running in parallel in the lamina propria and about 20% of those in the submucosa, and is a terminal blood supply site for esophageal varices.

Ordinary esophageal varices (Fig. 5.3): Usually, four esophageal varices are formed in the submucosal layer superior to and fed by these palisading veins (96%). These four varices have branching communications one another. In individuals without portal hypertension, blood in the palisade zone is circulated by the act of breathing and other factors into both the thoracic and abdominal directions. With increased portal pressure, the flow becomes hepatofugal; but for esophageal varices, the palisade zone remains an important buffer area against high-pressure portal venous backflow.

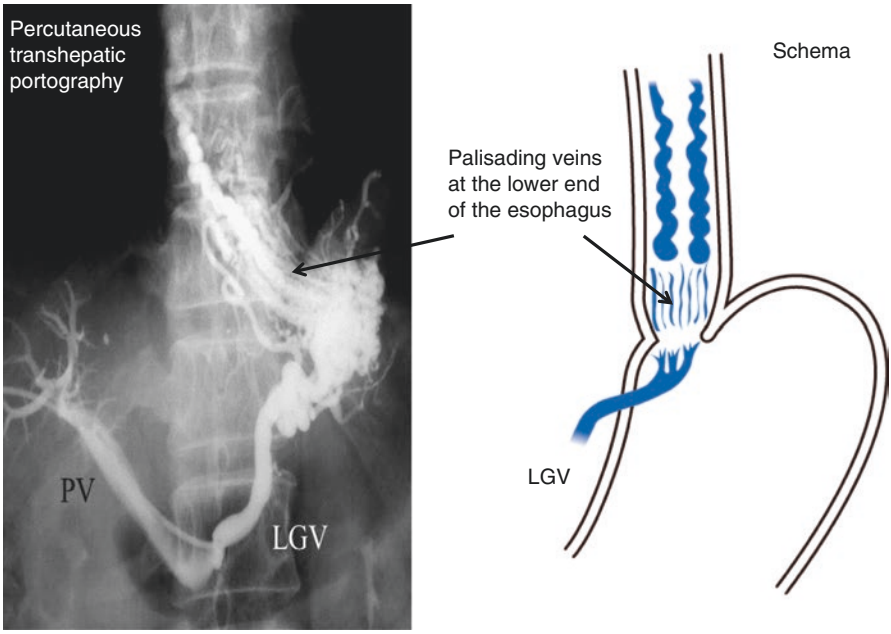


Fig. 5.3 Ordinary esophageal varices (96%). *PV* portal vein, *LGV* left gastric vein (feeding vessel)

5.4.1 Endoscopic Treatment-Resistant Varices

Pipeline stem varix of the esophagus (Fig. 5.4): An exceptional varix type without palisade veins (4%), which is a pipeline stem varix [16], is associated with higher internal pressure and higher blood flow volume than those of ordinary esophageal varices, because the pipeline varix has no palisading veins to neutralize high-pressure portal venous backflow, which is difficult to treat endoscopically when not preoperatively diagnosed [17]. Endoscopic injection sclerotherapy (EIS) with endoscopic balloon and endoscopic variceal ligation (EVL) with a pneumatic EVL device (Sumitomo Bakelite, Tokyo, Japan) at a time are highly recommended for the treatment of pipeline varix to prevent post-procedure bleeding.

The simultaneous EIS and EVL performance, termed EISL (Fig. 5.5), is of greater advantage to post-bleeding prevention from the needle puncture site than EIS alone.

Large isolated gastric fundal varices (IGFVs) (cf. Figs. 5.1 and 5.7): Among endoscopic treatments for large IGFVs, *n*-butyl-2-cyanoacrulate (tissue adhesive glue) injection showed good results in the literatures [18, 19] and has been recommended by the report of the Baveno VI Consensus Workshop in 2015 [20].

Special types of varices without systemic portal hypertension include upper or middle esophageal downhill varices due to superior vena caval or azygos venous obstruction and gastric varices caused by pancreatic cancer-associated splenic venous occlusion.

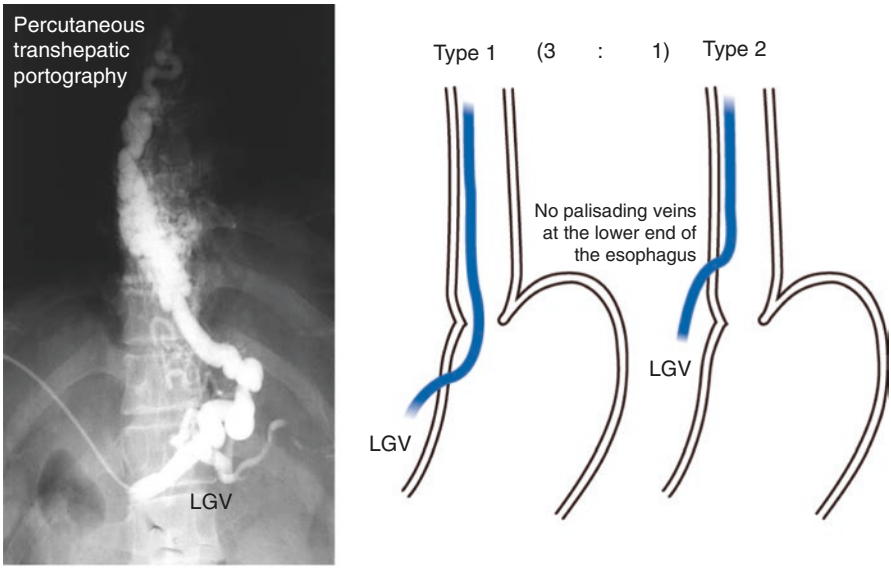


Fig. 5.4 Pipeline stem varix of the esophagus (4%). *LGV* left gastric vein (feeding vessel)

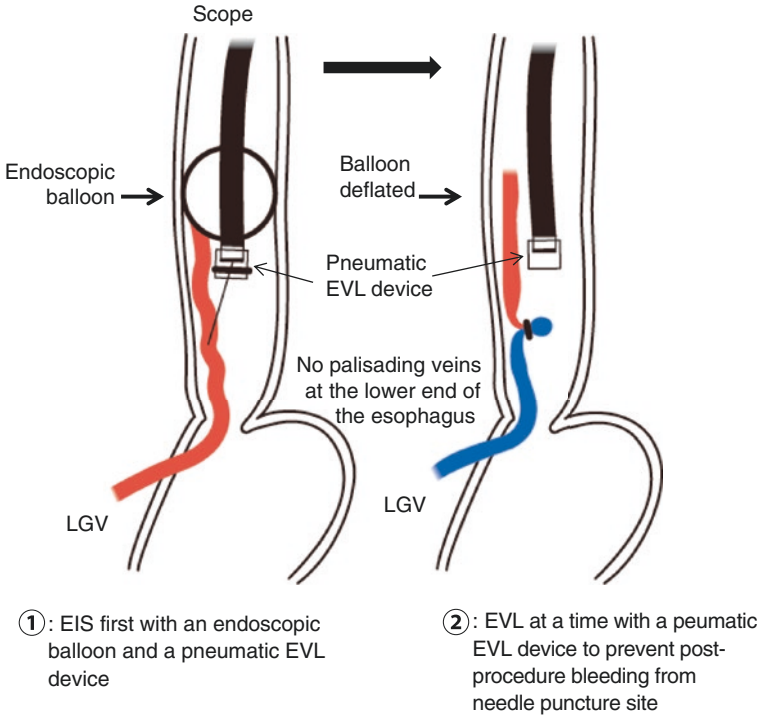


Fig. 5.5 Simultaneous EIS with endoscopic balloon and EVL with pneumatic device: EISL for pipeline stem varix. *EIS* endoscopic injection sclerotherapy, *EVL* endoscopic variceal ligation, *EISL* EIS + Ligation, *LGV* left gastric vein

5.4.2 Correlation of Portal Pressure and Hepatic Function with the Development of Varices

In liver cirrhosis, a portal pressure of ≥11–12 mmHg may indicate the presence of esophageal varices [21, 22]. However, no correlation has been found between variceal size and portal pressure. The Child-Pugh score is known to be closely related to the size of esophageal varices but not to that of IGFVs [22, 23]. More advanced esophageal varices may accompany more advanced cirrhosis.

On the other hand, IGFVs are more associated with abnormal portal venous flow, and with the presence of major splenorenal (S-R) shunting in particular, than with hepatic dysfunction. They tend to be accompanied by recurrent shunt encephalopathy due to the S-R shunt. In IGFVs, porto-systemic shunting commonly occurs, with cases having an S-R shunt showing lower portal pressure than those without an S-R shunt. Some cases are free of, or with only a mild degree of, esophageal varices. These observations indicate a significant drainage effect of S-R shunt, which is perceived to be an endoscopic IGFV.

5.4.3 Blood Supply Routes for Esophagogastric Varices

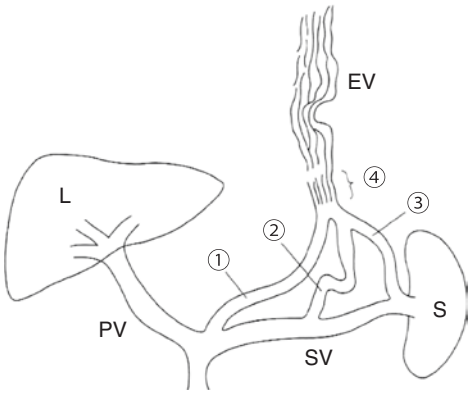
A portographic study of esophageal varices revealed that in all the cases examined, the left gastric vein was the main supply route for the varices, feeding them ultimately through palisading veins. In addition to the left gastric vein, posterior and short gastric veins were observed to be also well developed and involved in the formation of varices. However, none of the cases had either short or posterior gastric veins alone supplying esophageal varices (Fig. 5.6) [15].

Gastric variceal supply routes include mainly the short and posterior gastric veins, followed infrequently by the left gastric veins. Gastric varices have no palisade zone, that is, a buffer area against portal venous backflow. Therefore, in gastric varices with S-R shunting, the blood flow volume is high, directly reflecting the portal flow volume.

5.4.4 Endoscopic Findings and Blood Supply Routes of Gastric Varices

In this section, endoscopic findings are described according to the "General Rules for Recording Endoscopic Findings of Esophagogastric Varices" (second edition) by the Japan Society for Portal Hypertension [24].

Feeding veins of gastric varices can be estimated based on endoscopic findings [25] as follows: Varices on the lesser curvature and/or anterior wall of the gastric cardiac region (Lg-c) are supplied by the left gastric vein and communicate with esophageal varices, many of which are without S-R shunts. On the other hand,



Feeding vein	n	(%)
LGV	27	(41)
LGV + PGV	22	(34)
LGV + SGV	13	(20)
LGV + PGV + SGV	3	(5)
Total	65	(100)

Fig. 5.6 Feeding veins of esophageal varices [15]

varices on the greater curvature and/or posterior wall of the gastric cardia extending from the cardiac area through the fundus (Lg-cf) or confined to the gastric fundus (Lg-f) are supplied mainly by short and/or posterior gastric veins, and S-R shunts are present in many cases (Table 5.2). IGFVs (Lg-f, Lg-cf) are supplied commonly by short or posterior gastric veins and infrequently by the left gastric vein. IGFVs are nearly always associated with S-R shunts and usually do not communicate with the esophageal varices.

Generally, the term IGFVs refers not only to gastric varices macroscopically confined to the gastric fundus but also to those that do not hemodynamically communicate with esophageal varices.

5.5 Treatment and Portal Hemodynamics of Esophagogastric Varices

If esophageal varices serving as collaterals are obliterated by EIS [26] or EVL [27], or if gastric varices serving as collaterals are eradicated by EIS or balloon-occluded

Table 5.2 Endoscopic locations and portographic feeding veins of gastric varices

Endoscopic findings	Portographic findings				
Gastric variceal location (Lg)	Major feeding vein			Communication with esophageal varices (%)	Communication with S-R shunt (%)
	LGV	PGV	SGV		
Lg-c, LC, AW ($n = 30$)	29	0	1	100.0	16.7
Lg-c, PW, GC ($n = 18$)	2	5	11	44.4	66.7
Lg-cf ($n = 2$)	0	1	1	0.0	100.0
Lg-f ($n = 6$)	0	1	5	0.0	100.0
Total ($n = 56$)	31	7	18	67.9	44.6

Lg-c adjacent to the cardiac orifice, *Lg-cf* extending from the cardiac orifice to the fornix, *Lg-f* localized to the fornix, *LC* lesser curvature, *GC* greater curvature, *AW* anterior wall, *PW* posterior wall, *LGV* left gastric vein, *PGV* posterior gastric vein, *SGV* short gastric vein, *S-R shunt* spleno-renal shunt [24, 25]

retrograde transvenous obliteration (B-RTO) [28], portal hemodynamics will alter. B-RTO, in particular, leads to massive S-R shunts together with IGFVs to be occluded and eliminated extensively, causing a marked improvement in the hemodynamic state, which some refer to as a portal reform.

5.5.1 Endoscopic Injection Sclerotherapy

EIS treatment of esophageal varices results in the disappearance or diminution of their blood supply routes; portal pressure increases and decreases in about 50% of cases each [29]. The presence of S-R shunts serves to inhibit portal pressure from increasing post-esophageal variceal treatment [29]. It is of interest that rectal varices were found more commonly among patients with a history of esophageal variceal treatment, as pointed out in the Japan Society for Portal Hypertension's report on their 2010 questionnaire survey about ectopic varices [30].

Awareness that a portopulmonary venous anastomosis constitutes a risky collateral is important [31, 32]. A sclerosant used for EIS may enter the left cardiac system, which then may trigger a sudden onset of myocardial or cerebral infarction.

5.5.2 Endoscopic Variceal Ligation

EVL is a procedure in which varices are mechanically ligated with rubber bands, which is aimed at obliterating the varices by organizing thrombi within them, leading to the healing and fibrosis of banded ulcers. Success rates for the blockage of variceal supply routes are low, and relapse rates are higher than that of EIS. Therefore, for the purpose of variceal recurrence prevention, consolidation therapy [33, 34] is recommended following EVL.

5.5.3 *Balloon-Occluded Retrograde Transvenous Obliteration*

B-RTO is a procedure developed in Japan to manage large IGFVs [28, 35]. Large IGFVs are approached retrogradely from the left renal vein, into which the S-R shunt drains blood, and a sclerosant is injected in IGFVs (Fig. 5.7). This procedure may also be called angiographic sclerotherapy or catheter sclerotherapy. B-RTO is markedly effective for total eradication of large IGFVs but only in the presence of S-R shunt. Despite this precondition, B-RTO is clinically highly useful, as S-R shunts are present in ≥96% of large IGFV cases (Figs. 5.8 and 5.9). B-RTO is also effective in treating shunt encephalopathy and ectopic varices, whenever inflow and outflow vessels are identified.

5.5.3.1 PSS Syndrome

The entity of PSS syndrome [35] (a.k.a. "portosystemic shuntopathy" [36, 37]) has been established by accumulated B-RTO case data. This is a new concept formed after B-RTO introduction that describes a constellation of symptoms caused mainly by extensive portal steal by S-R shunts, which are major PSSs. To date the conditions provided below, which are known to be relieved by B-RTO, have been identified to constitute the PSS syndrome.

- Otherwise called
  - angiographic sclerotherapy
  - catheter sclerotherapy
- Indication
  - IGFVs with splenorenal shunt
  - ectopic varices

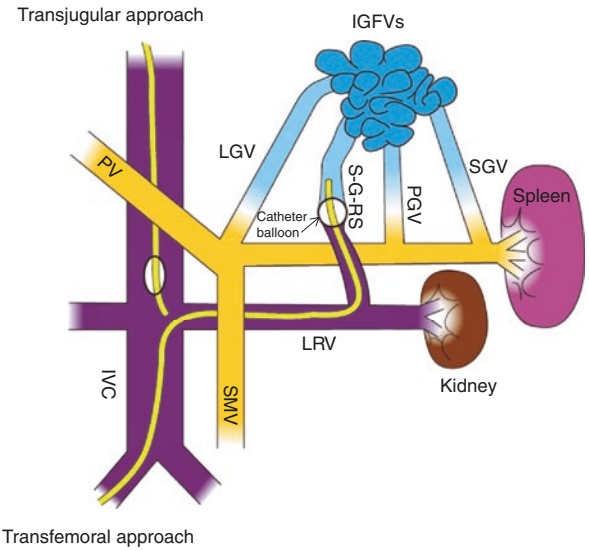


Fig. 5.7 Balloon-occluded retrograde transvenous obliteration: B-RTO. *IGFVs* isolated gastric fundal varices, *SGV* short gastric vein, *PGV* posterior gastric vein, *S-G-RS* spleno-gastro-renal shunt, *LGV* left gastric vein, *PV* portal vein, *IVC* inferior vena cava, *SMV* superior mesenteric vein, *LRV* left renal vein

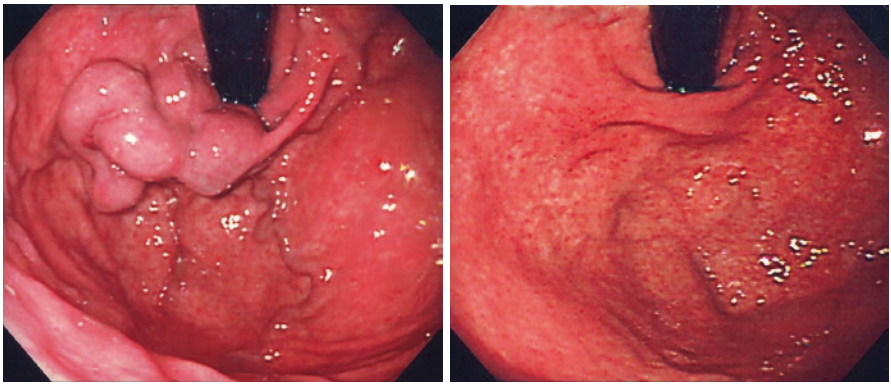


Fig. 5.8 Endoscopic views of large isolated gastric fundal varices (IGFVs) treated by a single session of balloon-occluded retrograde transvenous obliteration (B-RTO)

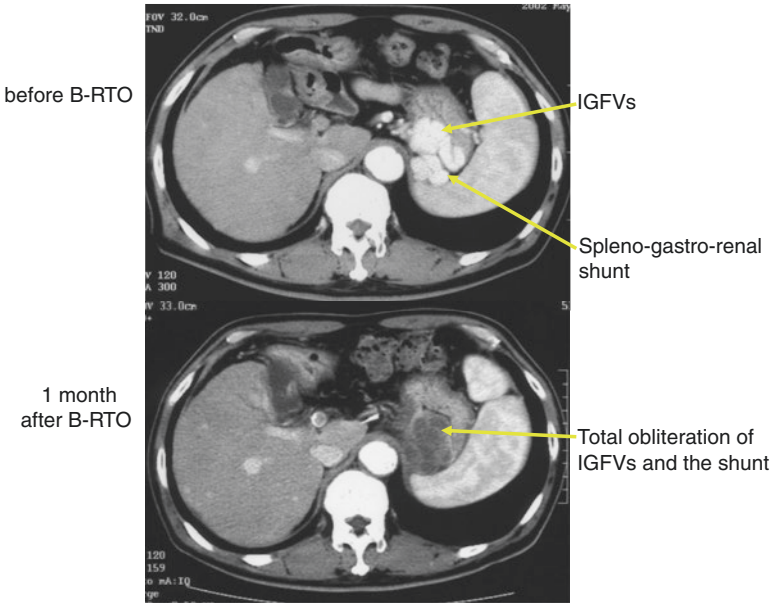


Fig. 5.9 Abdominal CT before and after B-RTO. *B-RTO* balloon-occluded retrograde transvenous obliteration, *IGFVs* isolated gastric fundal varices

- *Recurrent Hepatic Encephalopathy (So-called Shunt Encephalopathy)*
  This is well known as a classic PSS encephalopathy [38]. B-RTO is well indicated in the management of this condition [39].
- *Reduced Hepatic Reserve*
  B-RTO has been reported to improve hepatic reserve [40–42], demonstrating that some of the decline in the hepatic reserve can be reversed. The improvement has been shown by hepatocyte level data and clinical findings (Fig. 5.10) [41, 43]. Of the hepatic (advanced liver pathology) and portal (extensive portal steal) factors involved in liver dysfunction, the latter is improved by B-RTO, although the improvement may vary depending on whether the cause of portal hypertension is viral or nonviral. Improved liver function (inhibition of worsening) has been shown to be maintained at 3 years post B-RTO [35].
- *Abnormal Glucose Tolerance*
  In portal hypertensive patients with liver cirrhosis, glucose metabolism has been shown to be improved after B-RTO [44, 45]. Possible mechanisms include correction of conditions such as diminished muscle insulin sensitivity associated with high peripheral blood insulin levels due to S-R shunting and reduced glucose use in the liver owing to intrahepatic and extrahepatic shunts.
- *Other*
  The following are included: increased cardiac output, antidiuretic hormone abnormality, endotoxemia, and pulmonary arteriovenous shunts.
- *Point of No Return*

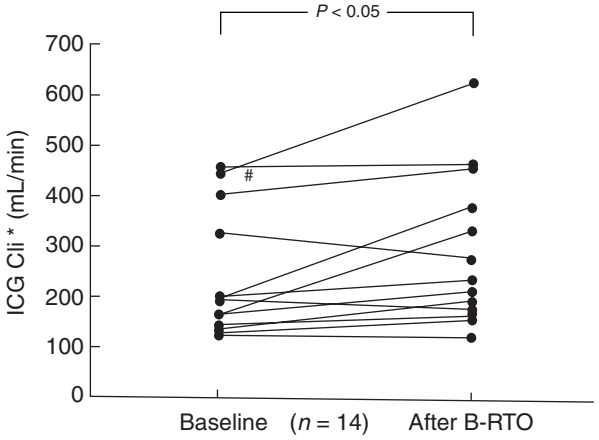


Fig. 5.10 Improvement of liver function by B-RTO. Intrinsic clearance of indocyanine green (ICG Cli) calculated by the catheterization and the continuous infusion of ICG methods significantly increased 4 weeks after balloon-occluded retrograde transvenous obliteration (B-RTO) ($p < 0.05$) [41]. #: The data of the patient with idiopathic portal hypertension. *ICG Cli is reported to directly represent the metabolic activity of hepatocytes in contact with purely functional blood flow in the sinusoidal perfusion model [42]

In some cases, hepatic function or other PSS syndrome is not improved post B-RTO. Rectification of extensive portal steal may not be beneficial depending on the degree and duration of hepatic parenchymal disorder. When reversible conditions turn irreversible (i.e., point of no return) remains unknown.

5.5.3.2 Increase In or Production of Esophageal Varices

Increase in or production of esophageal varices has been reported to be more common post B-RTO than post EIS. However, regarding this issue, more controlled studies and further accumulation of prospective evaluation data are needed.

5.6 Conclusion

Mechanisms of the development of portal hypertension and consequent esophagogastric varices are described based on findings obtained to date. The developmental and pathophysiological (hemodynamic) mechanisms of portal hypertension are issues closely related to its diagnosis and treatment, and sufficient understanding of these issues will lead to lifesaving rational treatments and favorable prognosis of this condition.

References

1. Kelty RH, Baggentoss AH, Butt HR, et al. The relation of the regenerated liver nodule to the vascular bed in cirrhosis. Gastroenterology. 1950;15:285–95.
2. Orrego H, Blendis LM, Crossley IR, et al. Correlation of intrahepatic pressure with collagen in the Disse space and hepatomegaly in humans and in the rats. Gastroenterology. 1981;80:546–56.
3. Marteau P, Ballet F, Chazouilleres O, et al. Effect of vasodilators on hepatic microcirculation in cirrhosis: a study in the isolated perfused rat liver. Hepatology. 1989;9:820–3.
4. Bathal PS, Grossmann HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. J Hepatol. 1985;1:325–37.
5. Skikuler E, Kravetz D, Groszmann RJ. Evolution of portal hypertension and mechanisms involved in its maintenance in a rat model. Am J Physiol. 1985;248(6 Pt 1):G618–25.
6. Benoit JN, Womack WN, Hernandez L, et al. “Forward and backward” flow mechanisms of portal hypertension. Relative contribution in the rat model of portal vein stenosis. Gastroenterology. 1985;89:1092–6.
7. Kiel JW, Oitts V, Benoit JN, et al. Reduced vascular sensitivity to norepinephrine in portal hypertensive rats. Am J Physiol. 1985;248:G192–5.
8. Levy M, Allotery JB. Temporal relationships between urinary salt retension and altered sysytemic hemodynamics in dogs with experimental cirrhosis. J Lab Clin Med. 1987;92:560–99.
9. Inokuchi K, Kobayashi M, Saku M, et al. Characteristics of splanchnic circulation in portal hypertension as analysed by pressure study in clinical cases. Kanzo. 1977;18:891–8. (Jpn with English summary).

10. Koyanagi N, Inokuchi K, Beppu K, et al. Hyperdynamic circulation in the left gastric venous area in patients with portal hypertension: angiological assessment. Jpn J Surg. 1985;15:134–9.
11. DeCarvalho CAF. Sur l'angio-architecture verineuse de la zone de transition oesophagogastrique et son interpretation fonctionellw. Acta Anat. 1966;64:125–6.
12. Arakawa M, Noda T, Kage M, et al. Clinicopathological studies of esophageal varices—the structure of blood vessels in esophageal wall. J Jpn Soc Gastroenterol. 1983;80:2339–46. (Jpn with English summary).
13. Noda T. Angioarchitectural study of the esophageal varices. With special reference to variceal rupture. Virchows Arch A Pathol Anat Histopathol. 1984;404:381–92.
14. Viannna A, Hayes PC, Moscoso G, et al. Normal venous circulation of the gastroesophageal junction. A rout to understanding varices. Gastroenterology. 1987;93:876–89.
15. Okubo K. The changes of portal collaterals in upper gastric area by endoscopic injection sclerotherapy (EIS). Acta Hepatologica Japonica. 1988;29:230–40. (Jpn with English summary).
16. Toyonaga A, Iwao T, Shigemori H, et al. Distinctive portal venographic pattern in patients with sclerotherapy resistant esophageal varices. J Gastroenterol Hepatol. 1996;11:1110–4.
17. Hamaguchi M, Higuchi K, Arakawa T, et al. Efficacy of combination of endoscopic variceal ligation with sclerotherapy on pipe-line varix: report of a case. Gastroenterol Endosc. 1999;41:65–71.
18. Soehendra N, Nam VC, Grimm H, et al. Endoscopic obliteration of large esophagogastric varices with Bucrylate. Endoscopy. 1986;18:25–6.
19. Oho K, Iwao T, Sumino M, et al. Ethanolamine oleate versus butyl cyanoacrylate for bleeding gastric varices: a nonrandomized study. Endoscopy. 1995;40:48–51.
20. de Franchis R, on behalf of the Baveno VI faculty. Expanding consensus in portal hypertension report of the Baveno VI consensus workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–52.
21. Garcia-Tsao E, Groszmann RJ, Fisher RL, et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology. 1985;5:419–24.
22. Iwao T, Toyonaga A, Sumino M, et al. Development of gastroesophageal varices and risk of variceal bleeding in patients with cirrhosis. Dig Endosc. 1991;3:485–90.
23. Cales P, Zabotto P, Meskens C, et al. Gastroesophageal endoscopic features in cirrhosis. Observation variability, interassociation, and relationship to hepatic dysfunction. Gastroenterology. 1990;98:156–62.
24. Tajiri H, Yoshida H, Obara K, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc. 2010;22:1–9.
25. Toyonaga A, Oho K, Tayama C, et al. Developmental mechanism of esophago -gastric varices. Surgery (Geka). 1992;57:627–33. (Jpn).
26. Hashizume M, Kitano S, Sugimachi K, et al. Endoscopic injection sclerotherapy for 1000 patients with esophageal varices: a 9-year prospective study. Hepatology. 1992;15:69–75.
27. Stiegmann GV, Cambre T, Sun JH. A new endoscopic elastic band ligation device. Gastrointest Endosc. 1986;32:230–3.
28. Kanagawa H, Mima S, Kouyama H, et al. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. J Gastroenterol Hepatol. 1996;11:51–8.
29. Toyonaga A, Iwao T, Sumino M, et al. Portal pressure after prophylactic sclerotherapy in patients with high risk varices. J Hepatol. 1994;21:515–20.
30. Watanabe N, Toyonaga A, Kojima S, et al. Current status of ectopic varices in Japan: results of a survey by the Japan Society for Portal Hypertension. Hepatol Res. 2010;40:763–76.
31. Sano A, Kuroda Y, Okuda K, et al. Portopulmonary venous anastomosis in portal hypertension demonstrated by percutaneous transhepatic cine-portography. Radiology. 1982;144:479–84.
32. Murakami K, Kokubu S, Yamagata S, et al. Endoscopic varicealography during injection sclerotherapy of porto-pulmonary venous anastomosis and its complications. Gastroenterol Endosc. 1982;34:2543–51. (Jpn with English summary).
33. Kitano S, Koyanagi N, et al. Prevention of recurrence of esophageal varices after endoscopic injection sclerotherapy with ethanolamine oleate. Hepatology. 1987;7:810–5.

34. Nakamura S, Mitsunaga A, Murata Y, et al. Endoscopic induction of mucosal fibrosis by argon plasma coagulation (APC) for esophageal varices: a prospective randomized trial of ligation plus APC vs. ligation alone. Endoscopy. 2001;33:210–5.
35. Kumamoto M, Toyonaga A, Inoue H, et al. Long term results of balloon-occluded retrograde transvenous obliteration for gastric fundal varices: hepatic deterioration links to portosystemic shunt syndrome. J Gastroenterol Hepatol. 2010;25:1129–35.
36. Toyonaga A. B-RTO: editorials. Jpn J Port Hypertens. 2001;7:122–8. (Jpn).
37. Shimizu Y, Kusano M. Portosystemic shunt. Kanzo. 2002;43:479–81. (Jpn).
38. Kato T, Umematsu T, Nishigaki Y, et al. Therapeutic effect of balloon-occluded retrograde transvenous obliteration on portal systemic encephalopathy in patients with liver cirrhosis. Intern Med. 2001;40:688–91.
39. Fukuda T, Hirota S, Sugimura K. Long term results of balloon-occluded retrograde transvenous obliteration for treatment of gastric varices and hepatic encephalopathy. J Vasc Interv Radiol. 2001;12:327–36.
40. Akahane T, Iwasaki T, Kobayashi N, et al. Changes in liver function parameters after occlusion of gastrorenal shunts with balloon-occluded retrograde transvenous obliteration. Am J Gastroenterol. 1997;92:1026–30.
41. Miyamoto Y, Oho K, Kumamoto M, et al. Balloon-occluded retrograde transvenous obliteration improves liver function in patients with cirrhosis and portal hypertension. J Gastroenterol Hepatol. 2003;18:934–42.
42. Ninoi T, Nishida N, Yamamoto Y, et al. Balloon-occluded retrograde transvenous obliteration of gastric varices with gastrorenal shunt: long term follow-up in 78 patients. Am J Roentgenol. 2005;184:1340–6.
43. Poupon RY, Poupon RE, Lebrec D, et al. Mechanisms for reduced hepatic clearance and elevated plasma levels of bile acids in cirrhosis. A study in patients with an end-to-side portacaval shunt. Gastroenterology. 1981;80:1438–44.
44. Hamano K, Shuichi S, Hisatomi K, et al. Metabolic and hormonal alterations observed after TIPS and B-RTO procedures in cirrhotic patients. Jpn Pharmacol Ther. 1998;26:109–14.
45. Tanabe N, Ishii M, Sato Y, et al. Effects of collateral occlusion on oral glucose tolerance test in liver cirrhosis. Dig Dis Sci. 2000;45:581–6.

Chapter 6
Mechanism and Pathophysiology of Bleeding from Esophagogastric Varices

Kazuhiko Oho

Abstract Bleeding from ruptured esophagogastric varices is the main complication of portal hypertension and a major cause of death. The risk factors of variceal bleeding have been reported but are still debated. Variceal hemorrhage can be caused by various factors including topical, portal hemodynamic, and systemic factors.

A hepatic vein pressure gradient (HVPG) of 10–12 mmHg is required for the development of varices. Furthermore, an HVPG > 12 mmHg is necessary for the occurrence of variceal hemorrhage. Factors that further increase variceal wall tension causing it to reach a threshold and develop a topical mucosal disorder of varices may induce variceal hemorrhage. Considering these factors, management of esophagogastric varices must be performed.

Keywords Esophagogastric varices · Variceal hemorrhage · Red color sign · Portal pressure · Variceal wall tension

6.1 Introduction

Esophagogastric variceal hemorrhage still remains a major problem in patients with liver cirrhosis and portal hypertension. The mechanism and pathophysiology of variceal hemorrhage remain controversial. Variceal hemorrhage can be caused by a wide range of factors including topical, portal hemodynamic, and systemic factors (Fig. 6.1).

K. Oho
Department of Gastroenterology and Hepatology, Yanagawa Hospital, Fukuoka, Japan

Kurume University School of Medicine, Fukuoka, Japan
e-mail: k-oho@yanagawa-hsp.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_6

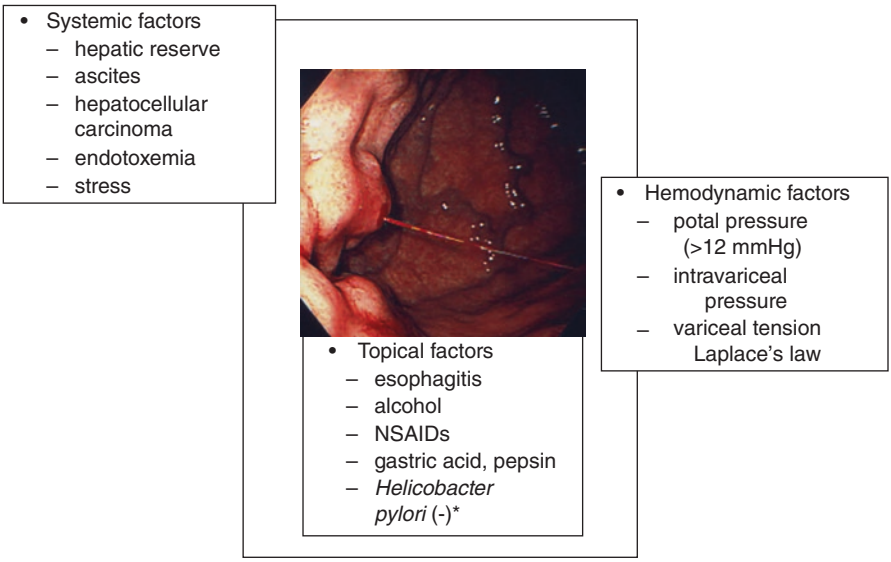


Fig. 6.1 Risk factors of variceal hemorrhage. Asterisk: From reference [7]. *NSAIDs*, nonsteroidal anti-inflammatory drugs

The aim of this chapter is to summarize the current understanding of the mechanical and pathophysiological aspects of variceal hemorrhage.

6.2 Topical Factors

6.2.1 Red Color Sign

Upper gastrointestinal endoscopy is the most useful procedure for diagnosing the presence of esophagogastric varices, predicting hemorrhage, or confirming the site of hemorrhage.

A red color sign (RC) is the most important finding for predicting hemorrhage from esophageal varices. The definition of RC on esophageal varices was first proposed in *The general rules for recording endoscopic findings on esophageal varices* [1], by the Japanese Research Society for Portal Hypertension, in 1980. In 1981, Beppu et al. [2] indicated that the presence of RC was particularly significant as an endoscopic finding predicting hemorrhage from esophageal varices. They reported that the incidence of hemorrhage was 70.1% in patients with varices in whom the grade of cherry red spot (CRS) or red wale marking (RWM) was evaluated as moderate to severe, being significantly higher than RC-negative or mild RC patients (15.4%). Although the incidence of hematocystic spot (HCS) was low, hemorrhage was observed in all patients with HCS, suggesting the close association between HCS and hemorrhage.

In 1988, the correlation between the presence of RC and esophageal variceal hemorrhage gained international recognition after The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices [3] published a report establishing RC on esophageal varices as predictive of hemorrhage.

On the other hand, factors such as large varices, RC on varices, and Child-Pugh classification (reduction of the hepatic reserve) are involved in hemorrhage from gastric fundal varices [4]. RC is not frequently observed in patients with gastric fundal varices, but its presence is a predictive factor for hemorrhage, as indicated in esophageal varices.

6.2.2 Esophagitis

Two hypotheses to explain the mechanism of variceal rupture have been proposed: the "explosion theory" and the "erosion theory." It is likened to a rubber balloon which may rupture if excessively inflated or pricked with a needle. The erosion theory proposed that variceal rupture resulted from external mucosal damage, such as erosion or ulcer, on the varices. However, the "erosion theory" is not accepted for the following reasons: the incidence of esophagitis is low in patients with hemorrhage [2]; and, pathologically, inflammatory cell infiltration in the sites of ruptured esophageal varices is not marked [5]. However, as shown in Fig. 6.2, there are some patients in whom esophagitis on varices may have caused rupture. Proton pump inhibitors (PPI) are very effective in inhibiting acid secretion and are extensively used in many acid related diseases. A randomized trial revealed that administration of PPI after esophageal variceal ligation reduces treatment failure and rebleeding

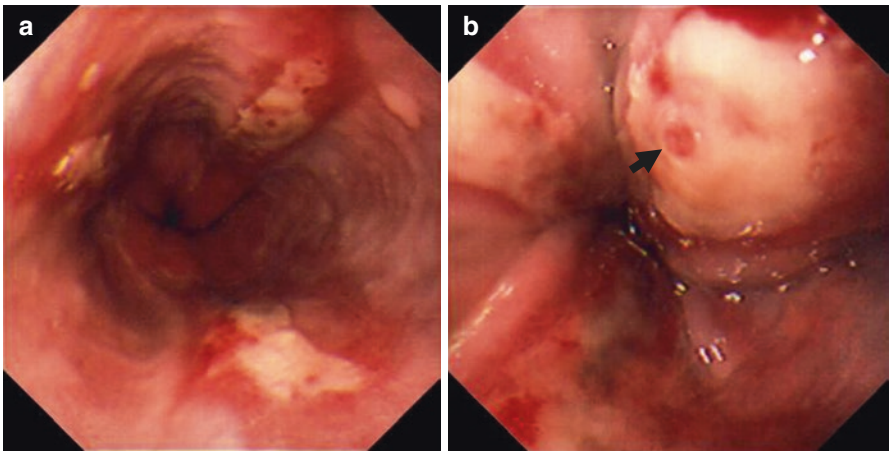


Fig. 6.2 Esophagitis on varices with multiple erosions and mucosal damage. (**a**) Erosive esophagitis was observed in the lower esophagus. (**b**) Rupture site (arrow) located at the center of erosion

[6]. Unfortunately, there is very limited published data on the prevention of initial variceal hemorrhage and rebleeding by administration of PPI.

6.2.3 Helicobacter pylori *Infection*

Sakamoto et al. [7] investigated the incidence of *Helicobacter pylori* infection in patients with esophagogastric varices and reported that the incidence of *Helicobacter pylori* infection in patients with hemorrhage was significantly lower than that in those without (Fig. 6.3). They also indicated that the pepsinogen I/II ratio, as a parameter of gastric acid secretion [8], was significantly higher in those with hemorrhage. These results suggest that *Helicobacter pylori* infection has a protective effect against esophagogastric variceal hemorrhage through the induction of atrophic gastritis and concomitant hypoacidity in patients with liver cirrhosis and portal hypertension. In the future, the influence of *Helicobacter pylori* eradication and effects of acid secretion inhibitor administration must be further examined.

6.2.4 *Nonsteroidal Anti-inflammatory Drugs*

Patients with liver cirrhosis have portal hypertensive gastropathy, that is, abnormal gastric mucosal hemodynamics in which congestion is involved. In the presence of this condition, gastric mucosa-protecting factors are reduced, and the incidence of ulcers and erosion is high; the gastric mucosa may be readily influenced by nonsteroidal anti-inflammatory drugs (NSAIDs) (Fig. 6.4).

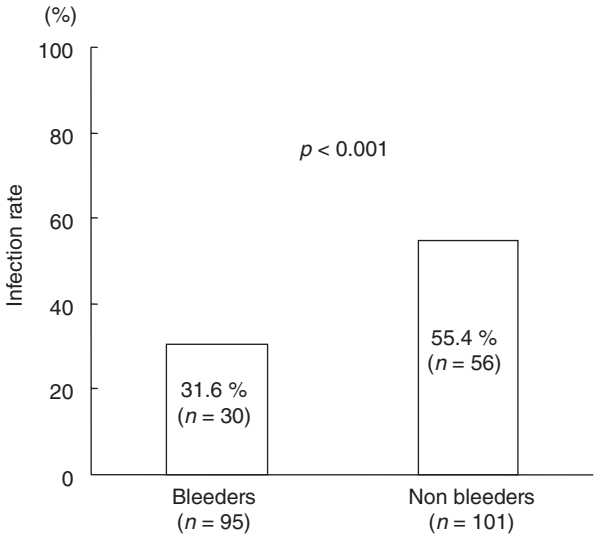


Fig. 6.3 *Helicobacter pylori* infection in patients with and without esophagogastric variceal hemorrhage ($n = 196$)

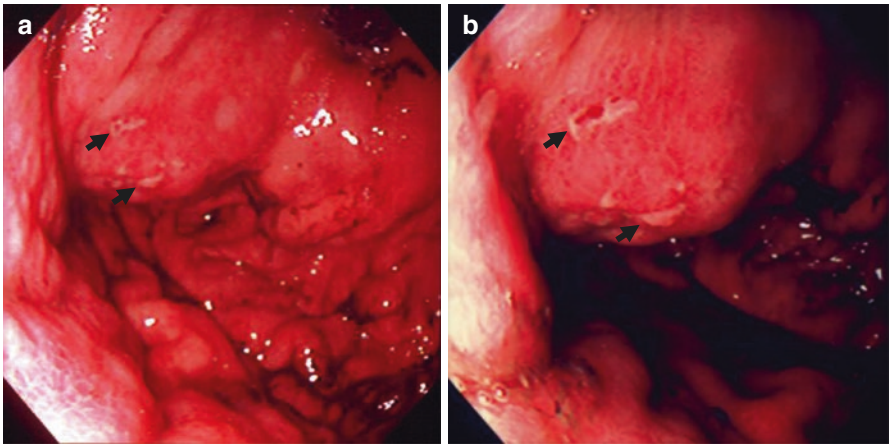


Fig. 6.4 Gastric variceal hemorrhage after NSAID use. (**a**) Multiple erosions and small ulcers (arrow) on bleeding gastric fundal varices. (**b**) Close view of rupture site

A case-control study suggested that cirrhotic patients who used NSAIDs were about three times more likely to have a first variceal bleeding episode than cirrhotic patients who did not [9]. The risk appeared to be due mainly to aspirin, either alone or combined with other NSAIDs, in patients with large varices.

Yoshida et al. [10] investigated the interactions between antiulcer drugs and NSAIDs, as related to bleeding esophagogastric varices in cirrhotic patients. Occasional oral NSAID use is an important step leading to variceal hemorrhage, especially in gastric fundal varices, even if the mucosa is protected by antiulcer drugs.

In the future, their association with hemorrhage from varices should be reviewed.

6.3 Portal Hemodynamic Factors

6.3.1 Portal Pressure

A portal pressure of 10–12 mmHg is required for the development of esophageal varices. Furthermore, the rupture of esophageal varices has been reported to occur at a hepatic venous pressure gradient (HVPG) of >12 mmHg [11].

Iwao et al. assessed portal pressure as the gradient between the portal venous pressure and free hepatic venous pressure, using the combined (portal vein and hepatic vein) catheterization technique. They also identified a portal pressure of 11 mmHg as necessary for the formation of varices and a portal pressure of >12 mmHg as necessary for variceal hemorrhage to occur [12] (Fig. 6.5).

On the other hand, huge gastric varices are usually associated with major splenorenal shunts, in which case, the portal pressure is lower than in patients with esophageal varices. Furthermore, hemorrhage from gastric varices frequently occurs even

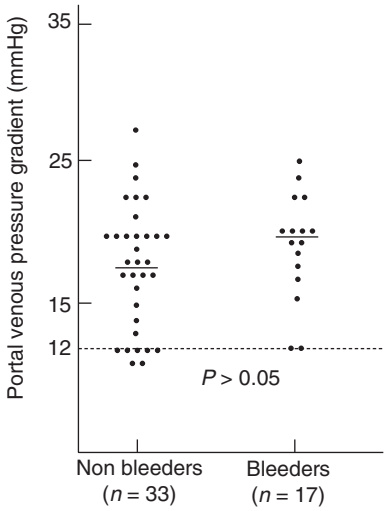


Fig. 6.5 Individual values of the portal venous pressure gradient in cirrhotic patients with and without a previous episode of hemorrhage

at an HVPG of <12 mmHg [13]. There may be no strong correlation between hemorrhage from giant gastric varices and the portal pressure, unlike hemorrhaging from esophageal varices.

There is circadian variation in portal pressure, and the rupture of varices frequently occurs from the evening to nighttime, when the portal pressure begins to increase [14]. On the other hand, diet or a postural change from standing to supine positions induces splanchnic hyperdynamic circulation, increasing the collateral pathway blood flow [15, 16]. Dinner or sleep may be involved in the rupture of varices.

6.3.2 Variceal Pressure

When calculating the wall tension of the varix using Laplace's law [17] (Fig. 6.6), the value in patients with hemorrhage from esophageal varices was two times higher than that in those without [18]. In other words, when varices have a high intravariceal pressure, a large diameter, and a thin wall, hemorrhage may occur. A study measured the esophageal intravariceal pressure by direct puncture and reported that the value of varices with RC was significantly higher than that of RC-free varices [19].

6.4 Systemic Factors

6.4.1 Hepatic Reserve

The risk of hemorrhage from varices is high in patients with severe hepatic reserve [3]. In the decompensated phase, the retention of ascites, reduction of blood

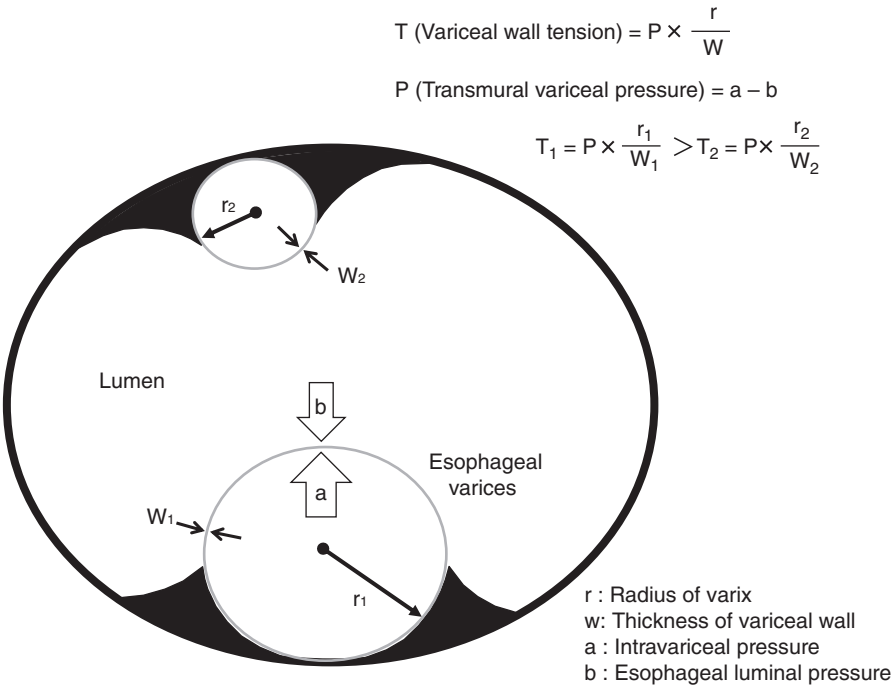


Fig. 6.6 Calculation of variceal wall tension according to Laplace's Law [17]

coagulation, and hypersplenism-related thrombocytopenia/endotoxemia occur, leading to variceal hemorrhage. In addition, once variceal hemorrhage occurs, it is difficult to achieve hemostasis.

6.4.2 Ascites

Luca et al. [20] measured the portal pressure, hepatic blood flow, and azygous blood flow by changing the abdominal pressure using a sandbag and indicated that an increase in the abdominal pressure decreased the hepatic blood flow, although there were no changes in the HVPG. They also reported that azygous blood flow, as a parameter of esophageal variceal blood flow, significantly increased, suggesting that tense ascites increases variceal blood flow, inducing hemorrhage from varices. Kravetz et al. reported that patients with ascites have significantly higher variceal pressure and wall tension than those without [21]. Therefore, ascites removal can be useful for reducing the risk of hemorrhage from varices [22].

6.4.3 Hepatocellular Carcinoma

In patients with advanced hepatocellular carcinoma, the development of portal tumor embolism or a hepatic arterio-portal shunt in addition to cancer-related compression or occlusion of the intrahepatic vascular bed markedly increases the portal pressure, increasing variceal blood flow as a collateral pathway. In such patients, varices rapidly become advanced and RC is marked, increasing the risk of hemorrhage. Furthermore, gastric mucosal disorder related to arterial embolization or arterial injection therapy for hepatocellular carcinoma may cause hemorrhage from gastric varices.

6.4.4 Alcohol Consumption

In alcohol cirrhotics, variceal hemorrhage occurs frequently. Recurrence or rebleeding after endoscopic treatment is also frequently observed. Chronic massive-volume alcohol consumption increases the intrahepatic vascular resistance, inducing esophagogastric mucosal damage. In addition, the incidence of bacterial infection which increases the portal pressure significantly increases. Endotoxemia, secondary to bacterial infection, may indeed be the critical trigger for variceal hemorrhage [23].

6.5 Conclusion

The mechanism of hemorrhage from esophagogastric varices is complex and remains to be clarified. Factors that cause an increase in intravariceal pressure to the threshold and topical mucosal disorder of varices may induce hemorrhage from varices.

References

1. Japanese Research Society for Portal Hypertension. The general rules for recording endoscopic findings on esophageal varices. Jpn J Surg. 1980;10:84–7.
2. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, et al. Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc. 1981;27:213–8.
3. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med. 1988;319:983–9.
4. Kim T, Shijo H, Kokawa H, Tokumitsu H, Kubara K, Ota K, et al. Risk factors for hemorrhage from gastric fundal varices. Hepatology. 1997;25:307–12.
5. Arakawa M, Kage M. The Anatomy and pathomorphology of esophageal varices. In: Okuda K, editor. Portal hypertension. Tokyo: Springer; 1991. p. 415–28.

6. Hidaka H, Nakazawa T, Wang G, Kokubu S, Minamino T, Takada J, et al. Long-term administration of PPI reduces treatment failures after esophageal variceal band ligation: a randomized, controlled trial. J Gastroenterol. 2012;47:118–26.
7. Sakamoto Y, Oho K, Toyonaga A, Kumamoto M, Haruta T, Inoue H, et al. Effect of *Helicobacter pylori* infection on esophagogastric variceal bleeding in patients with liver cirrhosis and portal hypertension. J Gastroenterol Hepatol. 2013;28:1444–9.
8. Iijima K, Sekine H, Koike T, Imatani A, Ohara S, Shimosegawa T. Serum pepsinogen concentrations as a measure of gastric acid secretion in *Helicobacter pylori*-negative and -positive Japanese subjects. J Gastroenterol. 2005;40:938–44.
9. Ledinghen VD, Heresbach D, Fourdan O, Bernard P, Liebaert-Bories M, Nousbaum J, et al. Anti-inflammatory drugs and variceal bleeding: a case-control study. Gut. 1999;44:270–3.
10. Yoshida H, Mamada Y, Taniai N, Mineta S, Kawano Y, Mizuguchi Y, et al. Interactions between anti-ulcer drugs and non-steroidal anti-inflammatory drugs in cirrhotic patients with bleeding esophagogastric varices. Hepatogastroenterology. 2009;56:1366–70.
11. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology. 1985;5:419–24.
12. Iwao T, Toyonaga A, Sumino M, Takagi K, Oho K, Sakaki M, et al. Development of gastroesophageal varices and risk of variceal bleeding in patients with cirrhosis. Dig Endosc. 1991;3:485–90.
13. Tripathi D, Therapondos G, Jackson E, Redhead DN, Hayes PC. The role of the transjugular intrahepatic portosystemic stent shunt (TIPSS) in the management of bleeding gastric varices: clinical and haemodynamic correlations. Gut. 2002;51:270–4.
14. García-Pagán JC, Feu F, Castells A, Luca A, Hermida RC, Rivera F, et al. Circadian variations of portal pressure and variceal hemorrhage in patients with cirrhosis. Hepatology. 1994;9:595–601.
15. Iwao T, Oho K, Sakai T, Sato M, Nakano R, Yamawaki M, et al. Upright posture decreases esophageal varices blood flow velocity in patients with cirrhosis. J Hepatol. 1998;28:447–53.
16. Iwao T, Oho K, Nakano R, Yamawaki M, Sakai T, Sato M, et al. Upright posture blunts postprandial splanchnic hyperemia in patients with cirrhosis and portal hypertension. J Gastroenterol. 1999;34:359–65.
17. Polio J, Groszmann RJ. Hemodynamic factors involved in the development and rupture of esophageal varices: a pathophysiologic approach to treatment. Semin Liver Dis. 1986;96:318–31.
18. Rigau J, Bosch J, Bordas JM, Navasa M, Mastair R, Kravetz D, et al. Endoscopic measurement of variceal pressure in cirrhosis: correlation with portal pressure and variceal hemorrhage. Gastroenterology. 1989;96:873–80.
19. Kleber G, Sauerbruch T, Fischer G, Paumgartner G. Pressure of intraoesophageal varices assessed by fine needle puncture: its relation to endoscopic signs and severity of liver disease in patients with cirrhosis. Gut. 1989;30:228–32.
20. Luca A, Cirera I, Garcia-Pagan JC, Feu F, Pizcueta P, Bosch J, et al. Hemodynamic effects of acute changes in intra-abdominal pressure in patients with cirrhosis. Gastroenterology. 1993;104:222–7.
21. Kravetz D, Bildzola M, Argonz J, Romero G, Korula J, Munoz A, et al. Patients with ascites have higher variceal pressure and wall tension than patients without ascites. Am J Gastroenterol. 2000;95:1770–5.
22. Kravetz D, Romero G, Argonz J, Guevara M, Suarez A, Abecasis R, et al. Total volume paracentesis decreases variceal pressure, size, and variceal wall tension in cirrhotic patients. Hepatology. 1997;25:59–62.
23. Goulis J, Armonis A, Patch D, Sabin C, Greenslade L, Burroughs AK. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. Hepatology. 1998;27:1207–12.

Chapter 7
Endoscopic Diagnosis of Esophagogastric Varices

Seishu Hayashi

Abstract A system for the precise evaluation and recording of esophagogastric varices is essential for the management of portal hypertension. General rules for recording endoscopic findings of esophageal varices were initially proposed in 1980 and revised in 1991. These rules have gradually been accepted and widely used in Japan and other countries. However, due to the development of endoscopic treatment (sclerotherapy and ligation) and interventional radiology for esophagogastric varices, the evaluation and recording of gastric varices as well as a description of mucosal changes after variceal treatment have been required, and several revised rules were proposed. The most recently revised rules are "The General Rules for Study of Portal Hypertension" (3rd edition (2013)), which comprise six main categories: location, form, color, red color sign, bleeding sign, and mucosal finding.

Keywords Endoscopic findings · Esophageal varices · Gastric varices · Red color sign · Portal hypertension

7.1 Introduction

As chronic liver disease advances and portal venous pressure increases, many portal-systemic collateral routes develop. Esophagogastric varices are part of the clinical manifestations of these portal-systemic collateral routes and can be observed directly beneath the esophageal and/or gastric mucosa on endoscopic examination. As the presence of esophagogastric varices not only shows the presence of portal hypertension but also presents a risk factor for bleeding from them, a system for

S. Hayashi
Division of Gastroenterology, Department of Internal Medicine, Tokyo Metropolitan Health and Medical Treatment Corporation Ookubo Hospital, Tokyo, Japan
e-mail: seishu-h@ga2.so-net.ne.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_7

precise evaluation and recording of esophagogastric varices is essential for the management of portal hypertension. In 1980, the Japanese Research Society for Portal Hypertension proposed a new system called "The General Rules for Recording Endoscopic Findings on Esophageal Varices" [1], mainly comprising five categories: fundamental color, red color sign, form, location, and erosion. However, since endoscopic diagnosis has been improved by the spread of video endoscopy replacing fiberscopes and the development of endoscopic treatments (sclerotherapy and ligation) and interventional radiology for esophagogastric varices, the evaluation and recording of gastric varices and the description of mucosal changes after variceal treatment have been required. Several revised rules were therefore proposed as "General Rules for Recording Endoscopic Findings of Esophagogastric Varices (1991)" [2] and "General Rules for Recording Endoscopic Findings of Portal Hypertension (2nd edition (2004))" [3]. The newest revised rules are "The General Rules for Study of Portal Hypertension (3rd edition (2013))" [4], comprising six main categories: location (L), form (F), color (C), red color sign (RC), bleeding sign (BS), and mucosal finding (MF) (Table 7.1).

7.2 Definition of Esophageal and Gastric Varices

The definition of esophageal and gastric varices based on endoscopy is a varix protruding from the esophageal or gastric mucosa under a sufficient supply of air. Dilated veins that flatten or disappear under a sufficient supply of air are thus not included as varices. In principle, endoscopic diagnosis is made based on endoscopic findings assessed via the video endoscopic system.

7.3 Endoscopic Diagnosis of Esophageal Varices

7.3.1 Location (L)

The longitudinal location of esophageal varices (EV) of different calibers is classified into three distinct regions: (1) locus superior (Ls), for varices located in the upper part of the esophagus; (2) locus medialis (Lm), for varices located in the middle part of the esophagus; and (3) locus inferior (Li), for varices located in the lower part of the esophagus. The boundary between the upper and middle parts of the esophagus is located at the height of the tracheal bifurcation. The boundary between the middle and lower parts of the esophagus is located at the middle line between the tracheal bifurcation and the esophagogastric junction. Although the tracheal bifurcation cannot be observed directly on endoscopy, that line can be predicted from the compress trace of the esophageal mucosa with the aortic arch and left main tracheal branch.

Table 7.1 General rules for recording endoscopic findings of esophagogastric varices (The General Rules for Study of Portal Hypertension, 3rd edn (2013) [4])

	Esophageal varices (EV)	Gastric varices (GV)
Category	Code subcategory	
Location (L)	Ls: locus superior	Lg-c: adjacent to the cardiac orifice
	Lm: locus medialis	Lg-cf: extension from the cardiac orifice to the fornix
	Li: locus inferior	Lg-f: isolated in the fornix
		Lg-b: located in the gastric body
		Lg-a: located in the gastric antrum
Form (F)	F0: no varicose appearance (red vein, blue vein)	
	F1: straight, small-caliber varices	
	F2: moderately enlarged, beady varices	
	F3: markedly enlarged, nodular, or tumor-shaped varices	
Color (C)	Cw: white varices	
	Cb: blue varices	
	Cw-Th: thrombosed white varices (white code)	
	Cb-Th: thrombosed blue varices (bronze varices)	
Red color sign (RC)	RWM: red wale markings	
	CRS: cherry red spots	
	HCS: hematocystic spots	
	RC0: absent	RC0: absent
	RC1: small in number, localized	RC1: with RC
	RC2: intermediate	
	RC3: large in number, circumferential	
	Te: telangiectasia	
Bleeding sign (BS)	Gushing bleeding	
	Spurting bleeding	
	Oozing bleeding	
	Red plug	
	White plug	
Mucosal finding (MF)	E: erosion	
	Ul: ulcer	
	S: scar	

Modified from The Japan Society for Portal Hypertension [4]

7.3.2 Form (F)

EV are classified into four groups according to shape and size: (1) F0 means lack of a varicose appearance. This classification is useful for documenting the disappearance of EV in response to treatment, even if red or blue veins are present. (2) F1 means straight and small-caliber varices. Small venous dilatations that disappear on insufflation of the esophagus are not included in this subgroup. (3) F2 means moderately enlarged, beady varices (Fig. 7.1). (4) F3 means markedly enlarged, nodular,

or tumor-shaped varices. The largest F-number is recorded as a representative F-number if several EV with different shapes and sizes are observed.

7.3.3 Color (C)

The color of EV is classified into two subcategories: (1) white varices (Cw) are whitish colored and look like large folds of esophageal mucosa (Fig. 7.1); (2) blue varices (Cb) are bluish-white or cyanotic colored (Fig. 7.2). The esophageal mucosa overlying Cb appears very thin. High-risk Cb are characterized by a fully expanded

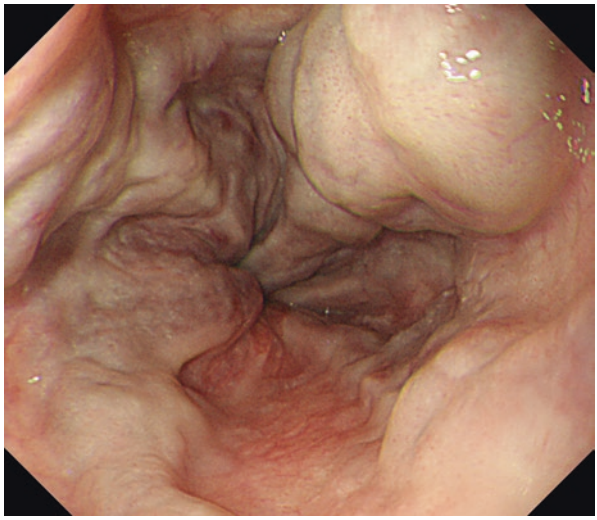


Fig. 7.1 F2, white varices (F2, Cw)

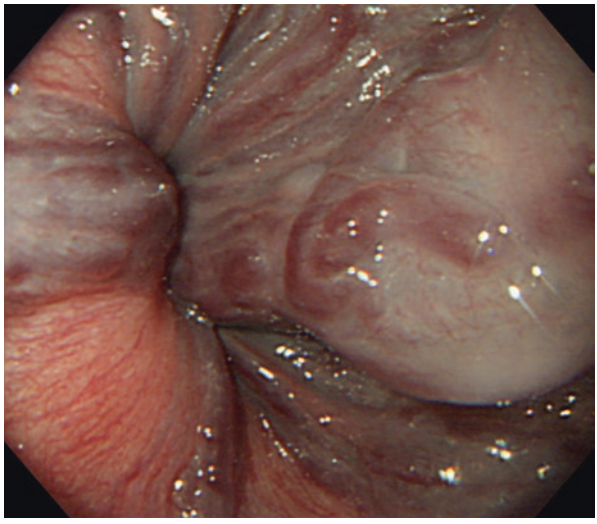


Fig. 7.2 F2, blue varices with RWM (F2, Cb, RC2 (RWM))

appearance with a glossy surface, similar to that of an over-inflated balloon. Cb that have become purple or violet because of increased variceal pressure and thinning of the mucosa are recorded by adding a "v" (violet) to their color (Cbv). Thrombosed varices after treatment are indicated by adding Th (thrombosis) to their color (i.e., Cb-Th or Cw-Th). Cb-Th, as so-called bronze varices [5], are varices obliterated by thrombus, and Cw-Th, so-called white cord, mainly comprises the variceal wall following absorption of thrombus. The color of the largest varix is recorded as a representative color if differently colored varices are observed.

In the anatomy of the normal venous circulation, palisade veins of the lower esophagus are composed of red veins and blue veins, and are distributed uniformly, in close proximity to each other and running parallel and longitudinally [6, 7]. Blue veins usually run under red veins, and these two veins run within the lamina propria of the mucosa, with the exception of a relatively small number of veins that remain within the submucosa. As portal venous pressure increases, blue veins running within the lamina propria in the palisade zone become dilated, resulting in F1 or F2 blue varices, and the red veins running above the blue varices swell and wind around, resulting in RCs or small-caliber crimson-red colored varices. Veins located within the submucosa are markedly dilated, resulting in F2 or F3 white varices [8].

7.3.4 Red Color Sign (RC)

RC refers to reddish changes seen immediately beneath the mucosal surface of the EV and is classified into three subcategories: (1) red wale marking (RWM) indicates a dilated venule oriented longitudinally on the mucosal surface of the EV, somewhat like wale or whip marks (Fig. 7.2); (2) cherry-red spot (CRS) indicates small red spots on the mucosal surface; and (3) hematocystic spot (HCS) indicates large, round, hemispherical crimson-red projections that look like blood blisters. RC are graded as 0, 1, 2, or 3 according to their density and distribution: (1) RC0 means absent; (2) RC1 means small in number and localized; (3) RC2 means intermediate between RC1 and RC3; and (4) RC3 means large in number and circumferential. The presence of telangiectasia is noted as Te. The RC subcategory (RWM, CRS, and/or HCS) is stated in parentheses after the RC grade. RC in patients presenting with F0 is recorded as F0, RC1–3.

Bleeding from EV is most often associated with RC [9, 10], and RCs are the most important predictors of variceal bleeding [11]. Thinning of the venous epithelium as a result of compression from dilated veins located in the lamina propria mainly produces the RC. Therefore, the varices easily rupture in these critical areas corresponding with the change in portal pressure or erosive change of the mucosa [8]. Most RWM and CRS are demonstrated as dilated and winding red veins running above the submucosal varices (varices on top of varices [9]), and some HCS are demonstrated as local cystic protrusions of part of the submucosal varices [12, 13]. Telangiectasia mainly comprises dilated red veins running within the lamina propria like RWM and is not only one of the predictors of variceal bleeding like RC

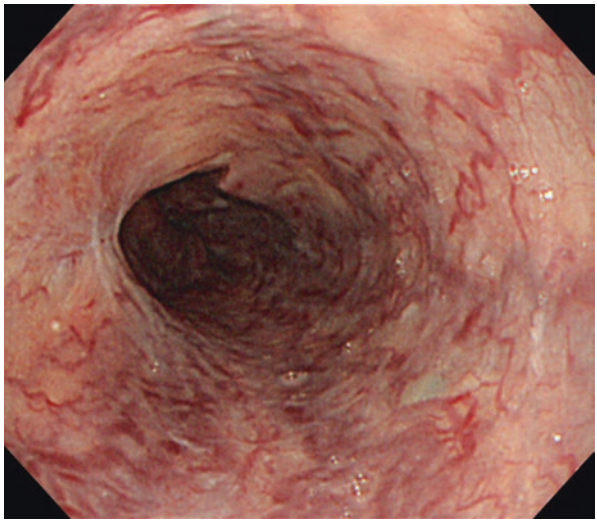


Fig. 7.3 Recurrent telangiectasia with RWM (F0, RC3 (RWM), S, Te)

but also one of the important forms of recurrence after endoscopic treatment [13] (Fig. 7.3). If EV with RC are observed on endoscopy, measures should immediately be examined to prevent bleeding from EV.

7.3.5 Bleeding Sign (BS)

Bleeding signs are divided into those found during bleeding and those found after hemostasis. Findings during bleeding are classified as gushing, spurting (Fig. 7.4), or oozing. If these findings are found, urgent treatment for hemostasis should be started as soon as possible. Findings after hemostasis are classified as red plug or white plug. Red plug is frequently observed within 2 days after hemostasis, and white plug is often observed within nearly 7 days after hemostasis. Although these two kinds of plug indicate hemostasis has been achieved, measures to prevent rebleeding should be promptly examined, because rebleeding often occurs.

7.3.6 Mucosal Finding (MF)

Mucosal findings are classified into three subcategories: (1) erosion (E), erosion or white moss adhesion on the mucosa of EV; (2) ulcer (Ul), ulcer on the esophageal mucosa caused by endoscopic treatment; and (3) scar (S), ulcer scar after endoscopic treatment.

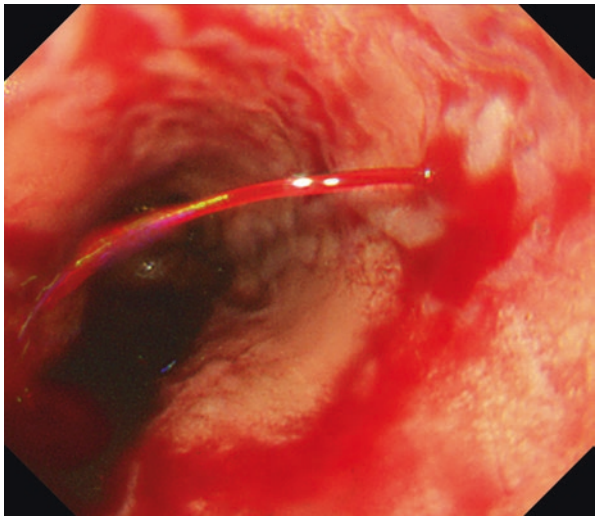


Fig. 7.4 Spurting bleeding from the esophageal varices

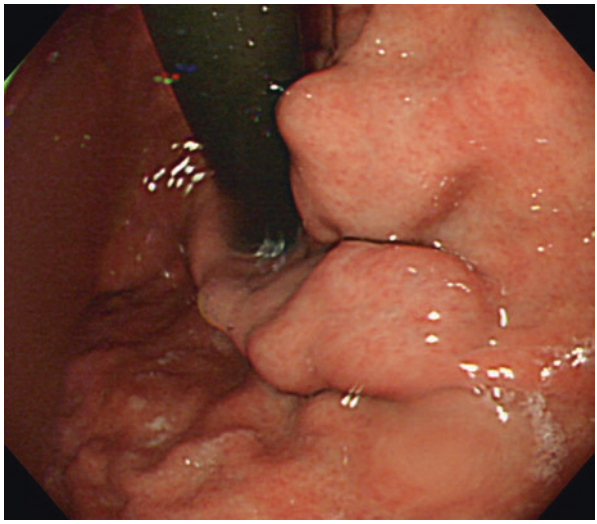


Fig. 7.5 Gastric varices adjacent to the cardiac orifice (Lg-c, F3, Cw)

7.4 Endoscopic Diagnosis of Gastric Varices

7.4.1 Location (L)

The locations of gastric varices (GV) are classified into five groups based on the relationship with the cardiac orifice: (1) Lg-c, varices adjacent to the cardiac orifice (Fig. 7.5); (2) Lg-cf, varices extending from the cardiac orifice to the fornix; (3) Lg-f, varices localized in the fornix (Fig. 7.6); (4) Lg-b, varices located in the body of the stomach; and (5) Lg-a, varices located in the antrum. This classification is based on the relation between the location and the blood supply route for the GV [14].

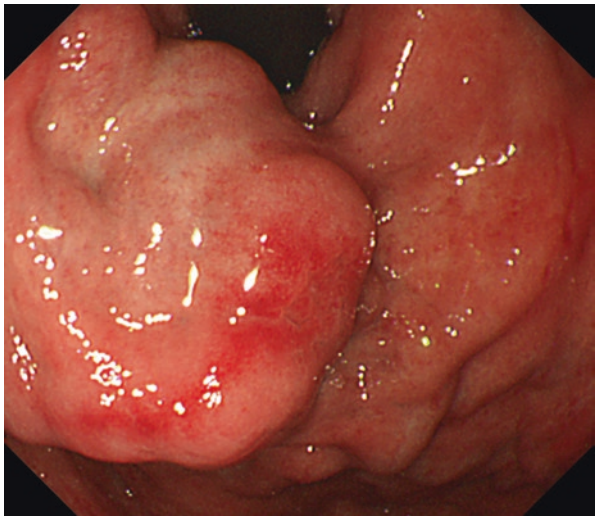


Fig. 7.6 Gastric varices localized to the fornix with RC (Lg-f, F3, Cw, RC1)

7.4.2 Form (F)

The same codes used to describe form in EV are used for GV.

7.4.3 Color (C)

The same codes used to describe color in EV are used for GV.

7.4.4 Red Color Sign (RC)

RC is graded as 0 or 1: (1) RC0 means absent and (2) RC1 means GV with RWM, CRS, and/or HCS.

Although reddish lesions observed on the mucosal surface of GV look like the RCs on the surface of EV, their histopathological backgrounds are different. In cases with a past history of bleeding from GV, the bleeding point of the GV is seldom observed as a gastric ulcer or HCS-like lesion with defect or thinning of the superficial gastric mucosa (Fig. 7.6). Red spots can be observed at high frequency on the surrounding gastric mucosa of such lesions. In cases without a past history of bleeding from GV, defects or thinning of the superficial gastric mucosa, erosion, ulcer, and red spots should be attended [15].

7.4.5 Bleeding Sign (BS)

The same codes used to describe bleeding signs in EV are used for GV.

7.4.6 Mucosal Finding (MF)

The same codes used to describe mucosal findings in EV are used for GV.

The appearance of exaggerated areae gastricae of the gastric mucosa after treatment is a useful endoscopic finding for evaluating therapeutic efficacy.

7.4.7 Risk Factors for Bleeding from GV

The risk factors for bleeding from GV are location (Lg-c or Lg-f), form, and presence of RC [16–18]. Lg-c frequently communicates with concomitant EV and can be dealt with as EV. In contrast, Lg-f are rarely associated with EV. The blood vessels that form Lg-f are found in the submucosal layer, but not in the lamina propria mucosae [19], and it is difficult to predict whether those Lg-f are at high risk of rupture or not based on the endoscopic findings, because the RCs, which are frequently observed on the surface of EV, are rarely observed on the surface of Lg-f. This peculiar structure is thought to be one of the causative factors for the relatively low incidence of bleeding from Lg-f. Lg-f are mostly associated with gastric renal shunts, and blood flow in Lg-f is abundant; therefore, bleeding from Lg-f is frequently more serious than that from EV or Lg-c.

7.4.8 Gastric Varices in Left-Sided Portal Hypertension

Left-sided (sinistral, or regional) portal hypertension (LSPH) is a clinical syndrome in the setting of splenic vein stenosis or obstruction (thrombosis) caused by pancreatic disorders such as acute or chronic pancreatitis or pancreatic neoplasms resulting in back pressure changes in the left portal system. LSPH is characterized as splenomegaly, normal hepatic function, and within the normal range of portal vein pressure and can lead to the formation of characteristic gastric varices extending from the greater curvature of the gastric body to the fornix, sometimes esophageal varices, and rarely rectal varices [20–23]. The development of LSPH has been recognized as an important cause of upper gastrointestinal bleeding resulting from gastric varices. According to the hemodynamics, splenic artery blood cannot flow back through the splenic vein because of the blockade of the splenic vein, and splenic artery blood shows reflux to the gastric mucosal veins through anastomosis with the

short gastric vein and left gastroepiploic vein and subsequent reflux to the portal vein through the left gastric vein and the right gastroepiploic vein. This results in reversal of flow in these veins and the formation of Lg-b, Lg-f, Lg-cf, and/or EV. Splenic artery blood occasionally shows reflux to the inferior mesenteric vein and subsequent reflux to the internal iliac veins through the rectal veins resulting in the formation of rectal varices. The hypertension in patient with LSPH is confined to the left side of the portal system and is therefore distinct from the common portal hypertension.

7.5 Recording of Varices and Evaluation of Treatment Effectiveness

Findings of EV and GV should be recorded in the order of the six main categories (L, F, C, RC, BS, and MS) as shown in the following examples. "Eradication" means the disappearance of varices after treatment, including thrombosed varices (F0, RC0). "Residue" means residual varices with F or RC after treatment. "Recurrence" means the reappearance of eradicated varices (F0, RC0) with F and/or RC. "Relapse" means the worsening of residual varices with F and/or RC.

Case 1 Spurting bleeding from nodular EV with RWM and CRS: Lm, F3, Cb, RC3 (RWM, CRS), BS (spurting bleeding)
Case 2 Recurrent telangiectasia with RWM: Li, F0, RC1 (RWM), S, Te
Case 3 EV and cardiac varices: Lm, F3, Cb, RC0, Lg-c, F2, Cw, RC0
Case 4 Spurting bleeding from GV extending from the cardiac orifice to the fornix: Lg-cf, F3, Cw, BS (spurting bleeding)
Case 5 Thrombosed blue varices with ulcer treated by endoscopic injection sclerotherapy: Lm, F2, Cb-Th, RC0, Ul
Case 6 Completely eradicated EV with ulcer scar: F0, RC0, S

References

1. Japanese Research Society for Portal Hypertension. The general rules for recording endoscopic findings on esophageal varices. Jpn J Surg. 1980;10:84–7.
2. Idezuki Y. General rules for recording endoscopic findings of esophagogastric varices (1991). Japanese Society for Portal Hypertension. World J Surg. 1995;19:420–2.
3. Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc. 2010;22:1–9.
4. The Japan Society for Portal Hypertension. The general rules for study of portal hypertension. 3rd ed. Tokyo: Kanehara & Co; 2013.
5. Yoshida T, Hayashi N, Nishimura S, Itoh T, Kawahara K, Okita K, et al. Mechanism of action of ethanolamine oleate used in injection sclerotherapy with special emphasis on the bronze varices. J Gastroenterol Hepatol. 1989;4(Suppl 1):173–5.

6. Noda T. Angioarchitectural study of esophageal varices. With special reference to variceal rupture. Virchows Arch A Pathol Anat Histopathol. 1984;404:381–92.
7. Vianna A, Hayes PC, Moscoso G, Driver M, Portmann B, Westaby D, et al. Normal venous circulation of the gastroesophageal junction. A route to understanding varices. Gastroenterology. 1987;93:876–89.
8. Arakawa M, Kage M. The anatomy and pathomorphology of esophageal varices. In: Okuda K, Benhamou J-P, editors. Portal hypertension—clinical and physiological aspects. Tokyo: Springer; 1991. p. 415–28.
9. Dagradi AE, Stempien SJ, Owens LK. Bleeding esophagogastric varices. An endoscopic study of 50 cases. Arch Surg. 1966;92:944–7.
10. Kleber G, Sauerbruch T, Ansari H, Paumgartner G. Prediction of variceal hemorrhage in cirrhosis: a prospective follow-up study. Gastroenterology. 1991;100:1332–7. S0016508591001737.
11. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, et al. Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc. 1981;27:213–8.
12. Ueki K. Histological study on red-color signs of esophageal varices. Tokyo Jikeikai Med J. 1985;100:1175–91.
13. Nakamura Y. Histopathological and endoscopic studies on esophageal varices with special reference to "red-color signs". Gastroenterol Endosc. 1985;27:17–25.
14. Watanabe K, Kimura K, Matsutani E, Matsutani S, Ohto M, Okuda K. Portal hemodynamics in patients with gastric varices: a study of 230 patients with esophageal and gastric varices using portal vein catheterization. Gastroenterology. 1988;95:434–40.
15. Hayashi S, Imamura J, Kimura K, Saeki S. Endoscopic findings of portal hypertension on Narrow Band Imaging: esophageal and gastric varices. Jpn J Port Hypertens. 2011;17:74–80.
16. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med. 1988;319:983–9.
17. Hashizume M, Kitano S, Yamaga H, Koyanagi N, Sugimachi K. Endoscopic classification of gastric varices. Gastrointest Endosc. 1990;36:276–80.
18. Kim T, Shijo H, Kokawa H, Tokumitsu H, Kubara K, Ota K, et al. Risk factors for hemorrhage from gastric fundal varices. Hepatology. 1997;25:307–12.
19. Masuzaki T. Clinicopathological study of the fundic varices—blood vessel structure in gastric paries. Nippon Shokakibyo Gakkai Zasshi. 1997;94:83–91.
20. Turrill FL, Mikkelsen WP. "Sinistral" (left-sided) extrahepatic portal hypertension. Arch Surg. 1969;99:365–8.
21. Belli L, Puttini M, Marni A. Extrahepatic portal obstruction: clinical experience and surgical treatment in 105 patients. J Cardiovasc Surg. 1980;21:439–48.
22. Thompson RJ, Taylor MA, McKie LD, Diamond T. Sinistral portal hypertension. Ulster Med J. 2006;75:175–7.
23. Li ZY, Li B, Wu YL, Xie QP. Acute pancreatitis associated left-sided portal hypertension with severe gastrointestinal bleeding treated by transcatheter splenic artery embolization: a case report and literature review. J Zhejiang Univ Sci B. 2013;14:549–54. https://doi.org/10.1631/jzus.B1200247.

Chapter 8
Diagnosis and Hemodynamics of Ectopic Varices

Norihito Watanabe, Seiichiro Kojima, and Shinji Takashimizu

Abstract Varices may form in any part of the gastrointestinal tract from the esophagus to the colon, when portal pressure increases. The most common site of ectopic varices is the rectum followed by the duodenum. Other sites of varices are the small intestine, colon, gall bladder, anastomotic site, and stoma. The incidence of rectal varices has been increasing in recent years. Patients have to be monitored for possible rectal varices especially after the treatment of esophageal and gastric varices. While cirrhosis is the most frequent underlying disorder in Japan, extrahepatic portal obstruction associated with thrombosis, tumor, or pancreatitis is common in the USA and Europe. Endoscopy to directly observe the variceal lesion is most frequently used for diagnosis. Computed tomography and magnetic resonance imaging are required for understanding the hemodynamic profiles of ectopic varices regardless of their sites. Ectopic varices may be fatal once bleeding occurs because of the high blood flow rate and volume. However, bleeding is considered infrequent in general. Ectopic varices are an important clinical issue in portal hypertension, and the incidence is expected to increase. The pathophysiology of ectopic varices needs to be elucidated to establish the diagnosis and treatment.

Keywords Ectopic varices · Diagnosis · Endoscopy · Diagnostic imaging
Collateral hemodynamics

8.1 Introduction

Portal pressure elevates due to the increase in vascular resistance of the intrahepatic portal veins and blood volume flowing into the liver [1, 2]. When portal pressure exceeds 200 mmH_2O, a variety of collateral vessels such as esophageal and

N. Watanabe (✉) · S. Kojima · S. Takashimizu
Division of Gastroenterology, Tokai University Hachioji Hospital, Hachioji, Tokyo, Japan
e-mail: norihito@is.icc.u-tokai.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_8

gastric varices, epigastric vein, splenorenal shunt, and gastrorenal shunt develop. Varices may form in any part of the gastrointestinal tract when portal pressure increases since the portal system is fed by venous blood flow in the gastrointestinal tract, from the stomach to the colon, and other abdominal organs. Although so-called ectopic varices other than esophageal and gastric varices are considered a relatively rare disorder, approximately 5% of all varices associated with gastrointestinal bleeding are identified as ectopic varices in the USA and European countries [3, 4]. The frequency and the site of ectopic varices are yet to be understood.

Endoscopic treatment for esophageal and gastric varices, i.e., endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL), has become established as the standard treatment in Japan over the past 20 years. Although treatment guidelines for esophageal and gastric varices have mostly been established [5], no consensus has been reached about the treatment of ectopic varices. With the advancement of diagnostic imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) in recent years, a variety of ectopic varices have been reported. This chapter outlines the diagnosis and the hemodynamics of ectopic varices, focusing on relatively frequent duodenal and rectal varices, in addition to the current status of ectopic varices in Japan.

8.2 Site of Varices

According to the Japanese nationwide survey in 1990, the frequency of ectopic varices was extremely low: 129 of 18,540 cases (0.7%) of all types of varices. Ectopic varices develop in a variety of organs, mainly in the gastrointestinal tract such as the duodenum, small intestine, colon, rectum, and gall bladder [6]. The survey in 2005 reported 57 of 173 cases (32.9%) of all ectopic varices were duodenal varices. There were two cases of duodenal varices in the duodenal bulb, 47 cases in the descending part and eight cases in the transverse part. Most of the duodenal varices were found in the descending to transverse part [7]. Small intestinal varices were reported in 11 cases: jejunal varices in seven cases, ileal varices in two cases, and varices in unknown sites in two cases. Colonic varices were reported in six cases. Rectal varices were the most common ectopic varices reported in 77 cases (44.5%), showing a significant increase from 20.2% reported 10 years earlier. Other reported sites of varices included the biliary tract in eight cases, anastomotic site in ten cases, stoma in three cases, and diaphragm in one case (Fig. 8.1). Lebrec et al. reported bleeding from ectopic varices in 1–3% of patients with portal hypertension, and 40% of the ectopic varices were found in the colon [8].

Duodenal varices were first reported by Alberti in 1931 [9]. The sites of duodenal varices are different between Japan and other countries because the hemodynamic profiles vary depending on the underlying disease. While the duodenal bulb is the most common site in the USA and Europe, varices are likely to develop in the descending or horizontal part of the duodenum in Japanese patients. Thirty-three

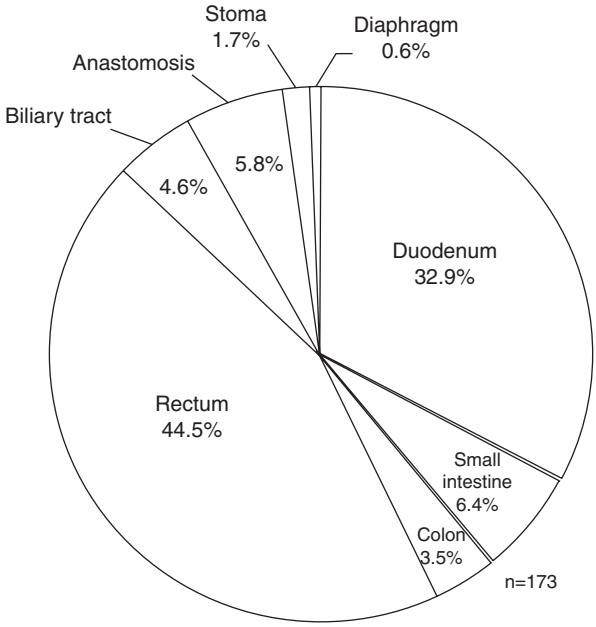


Fig. 8.1 Site of ectopic varices. Rectal varices are the most common ectopic varices (44.5%) followed by duodenal varices (32.9%). Other common sites of ectopic varices include the small intestine, colon, biliary tract, anastomosis, stoma, and diaphragm

cases of rectal varices were first reported in 1954 [10]. The frequency of rectal varices in patients with portal hypertension is roughly 10% or lower [11, 12]. On the other hand, Chawla et al. reported rectal varices in 78% of patients with portal hypertension. The incidence was 56% in patients with cirrhosis and as high as 89% in those with a non-cirrhotic liver [13].

8.3 Underlying Diseases

The most common disease underlying ectopic varices in Japan is cirrhosis, and it is found in approximately 80% of the patients. The causes of cirrhosis include hepatitis B virus, hepatitis C virus, alcohol, primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Type C cirrhosis takes up about a half of the diseases underlying ectopic varices. Non-cirrhotic diseases underlying ectopic varices include idiopathic portal hypertension (IPH) and extrahepatic portal vein obstruction (EHO) [7]. Although no apparent association is generally noted between the site of ectopic varices and the underlying disease, the majority of ectopic varices in patients with alcoholic cirrhosis are duodenal varices, and biliary varices are most common in patients with EHO. It has been reported that the site of duodenal varices may be associated with the underlying disease. While cirrhosis is the most common disease underlying duodenal varices in Japan, cirrhosis causes only about 30% of duodenal varices in other countries. EHO such as occlusion of the splenic vein or

superior mesenteric vein due to thrombosis, tumor, or pancreatitis is the common underlying disease reported overseas [9]. In duodenal varices, the difference in reported underlying disease between Japan and the USA and Europe may be associated with the site of varices.

Ectopic varices are accompanied by esophageal and gastric varices in 78.0% of patients overall. A strong association is suggested between ectopic varices and esophageal/gastric varices based on the high percentage of patients with esophageal varices recognized in their past history (76.9%) and those who have been treated (57.9%). Notably, a past history of esophageal varices was recognized in 73 (94.8%) of 77 cases of rectal varices. The percentage is apparently higher especially in patients with rectal varices compared with those with varices in other organs. The findings indicated that rectal varices were noted among patients having been treated for esophageal varices. Rectal varices should be anticipated after the treatment of esophageal varices [7]. Since the inferior mesenteric vein and the superior rectal vein are frequent as afferent vessels of rectal varices, descending collateral vessels are likely to develop after the treatment of esophageal and gastric varices that scleroses the ascending left, posterior, and short gastric veins, allowing rectal varices to form [14, 15]. Periodic rectal endoscopy should be required after the treatment of esophageal and gastric varices based on the high incidence of rectal varices after treatment.

8.4 Diagnostic Methods

8.4.1 Endoscopy

Endoscopy to directly observe the lesion is indispensable for diagnosing ectopic varices. Endoscopy is the most frequently used method of diagnosing ectopic varices. Upper gastrointestinal endoscopy is performed in approximately 90% of patients with duodenal varices. All rectal varices are diagnosed using lower gastrointestinal endoscopy. Double-balloon endoscopy and capsule endoscopy are now used to diagnose small intestinal varices. Medium and larger varices, i.e., form (F) 2 or greater varices according to the general rules for recording the endoscopic findings of esophageal varices [16], are frequently found in ectopic varices. There is no difference among the various ectopic varices with respect to the degree of color or form in endoscopic findings, while F2 or greater variceal lesions constituted more than 70% of the lesions in the duodenum, colon, and rectum. Varices positive for red color (RC) sign are found in 24% of duodenal cases and in 40% of rectal cases. Duodenal varices and rectal varices may exist extramurally and be generally less likely to bleed, but any enlarged or RC sign-positive rectal varices should be treated [11]. Matsui et al. pointed out that the F factor bears greater importance than RC sign-positive varices as a risk factor for bleeding from duodenal varices [17]. The propriety of prophylactic treatment for ectopic varices should be subject to further discussion because neither findings to predict hemorrhage nor any guidelines for treatment has been established.

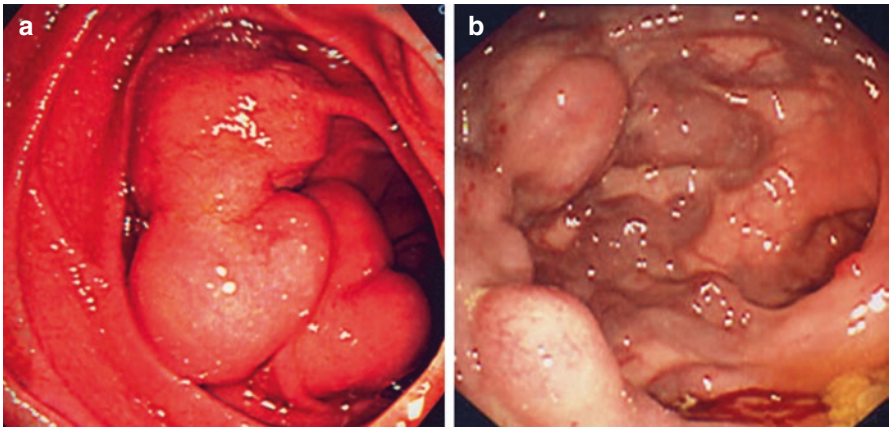


Fig. 8.2 Endoscopic findings of ectopic varices. (**a**). Duodenal varices, (**b**) Rectal varices. Both duodenal and rectal varices are recognized as elevated tumorous or tortuous submucosal lesions

Duodenal varices are often diagnosed with upper gastrointestinal endoscopy since most reported cases are hemorrhagic. Hemorrhagic varices are difficult to diagnose because of blood accumulation. They are usually protruded lesions with erosion and gushing blood. Duodenal varices were recognized as elevated tumorous or tortuous submucosal lesions (Fig. 8.2a). They may be difficult to differentiate from submucosal tumor. Only 44% of duodenal varices are accurately diagnosed with endoscopy [18]. It is important to exclude duodenal varices, nevertheless, in cases of upper gastrointestinal tract bleeding in liver cirrhosis. Varices are formed more frequently in the descending or transverse parts of the duodenum in Japan; thus the upper gastrointestinal tract must be explored down to deep parts in the duodenum.

Direct observation with an endoscope is the most useful diagnostic method for rectal varices. Colonic varices are usually localized in the rectum but may be found anywhere in the colon. The endoscopic findings are mostly the same as those of duodenal varices: elevated tumorous or tortuous submucosal lesions (Fig. 8.2b). Endoscopic ultrasonography (EUS) is a useful examination for diagnosing rectal varices and defining the hemodynamics. The variceal visualization rate of EUS is significantly higher compared with that with the regular endoscopy. The submucosal layer, the penetrating branches, and the extramural varix can be visualized [19]. In colonic varices, blue veins and arborescent vascular dilatation are visualized other than the varices.

8.4.2 MRI and CT Scan

Rapidly progressing in recent years, CT and MRI are used for diagnosing ectopic varices and understanding the hemodynamic profiles irrespective of the site of varices. With the emergence of magnetic resonance angiography (MRA), the portal veins are now noninvasively and easily visualized. MRA is an excellent tool for

defining collateral hemodynamics in portal hypertension. It is an important means of examination to evaluate the hemodynamics before and after the treatment of varices and to determine the indication and the efficacy of interventional radiology (IVR) [20]. In addition, MRA can visualize the entire portal vein system in the abdomen, and it is excellent in identifying ectopic varices such as duodenal and rectal varices and defining hemodynamics of the collateral vessels (Fig. 8.3).

CT angiography (CTA) with multidetector-row CT (MDCT) produces very high-quality images and reconstructs images in all sections including cross, sagittal, and coronal sections. With a higher resolution performance compared with MRA, CTA is excellent in visualizing small vessels and can take images in the arterial, portal, and venous phases (Fig. 8.4). The stereoscopic relationship between the collateral

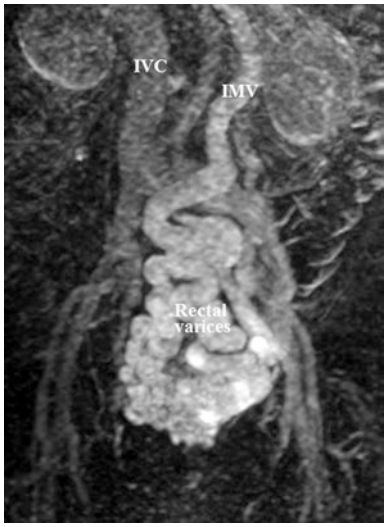


Fig. 8.3 MRA image of rectal varices. In rectal varices, the superior rectal vein branching out of the inferior mesenteric vein (IMV) serves as an afferent vessel. After rectal varices form, the blood flows into the inferior vena cava (IVC) through the internal iliac vein

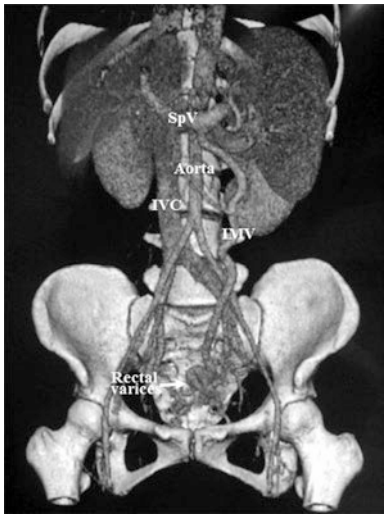


Fig. 8.4 CTA image of rectal varices. With a higher resolution performance, CTA visualizes three-dimensional images to clearly show the stereoscopic relationship of the varices, the afferent vessel (inferior mesenteric vein; IMV), and the efferent vessel. *IVC* inferior vena cava, *SpV* splenic vein

vessels and the varices is clearly visualized in three-dimensional images [21, 22]. The use of CTA is expected to increase to identify ectopic varices and understand the hemodynamic profiles.

8.4.3 Angiography

Collateral vessels should be thoroughly understood before treating ectopic varices since the hemodynamics are complicated in ectopic varices unlike in esophageal and gastric varices. Venous phase imaging of celiac and superior mesenteric artery or percutaneous transhepatic portography (PTP) has been used to visualize the portal veins. In portal hypertension, an increase in portal pressure is noted by measuring the hepatic venous pressure gradient (HVPG) [23], which is the difference between the wedge hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP). Portal hypertension is clinically defined as HVPG 10 mmHg or higher. The portal hypertension is considered severe when the HVPG is 12 mmHg [24]. Now that collateral hemodynamics are easily identified by MRA or CTA, abdominal angiography is commonly performed for not only diagnosis but also IVR. Various types of IVR including percutaneous transhepatic obliteration (PTO), balloon-occluded retrograde transvenous obliteration (B-RTO), and transjugular intrahepatic portosystemic shunt (TIPS) are performed for the treatment of ectopic varices [25–28]. An appropriate IVR is selected based on the hemodynamics recognized in each patient.

8.5 Hemodynamic Profiles

In portal hypertension, a variety of collateral vessels such as esophageal and gastric varices, epigastric veins, splenorenal shunt, and gastrorenal shunt develop. Gastric varices are fed by the left, short, and posterior gastric veins. The blood then flows into the left renal vein through the gastrorenal shunt. Identifying the efferent and afferent vessels of ectopic varices is very important to understand the pathophysiology and determine a treatment strategy. The hemodynamics in duodenal and rectal varices, which are relatively frequent ectopic varices, are described here (Fig. 8.5).

The most common afferent vessels of duodenal varices are the inferior pancreaticoduodenal vein (IPDV) followed by the superior mesenteric vein (SMV) (10.2%), other duodenal veins (DV), and superior pancreaticoduodenal vein (SPDV). The gonadal vein is the efferent vessels in the majority of cases. The hemodynamics in duodenal varices vary depending on the underlying disease of portal hypertension. In cirrhosis or posthepatic portal hypertension, the branches of SMV including IPDV, SPDV, and DV develop as hepatofugal routes and often form varices in the descending or horizontal limb of duodenum. In extrahepatic portal vein obstruction, collateral vessels such as the pancreaticoduodenal vein develop to form varices in the duodenal bulb region and then ascend hepatopetally into the liver [29].

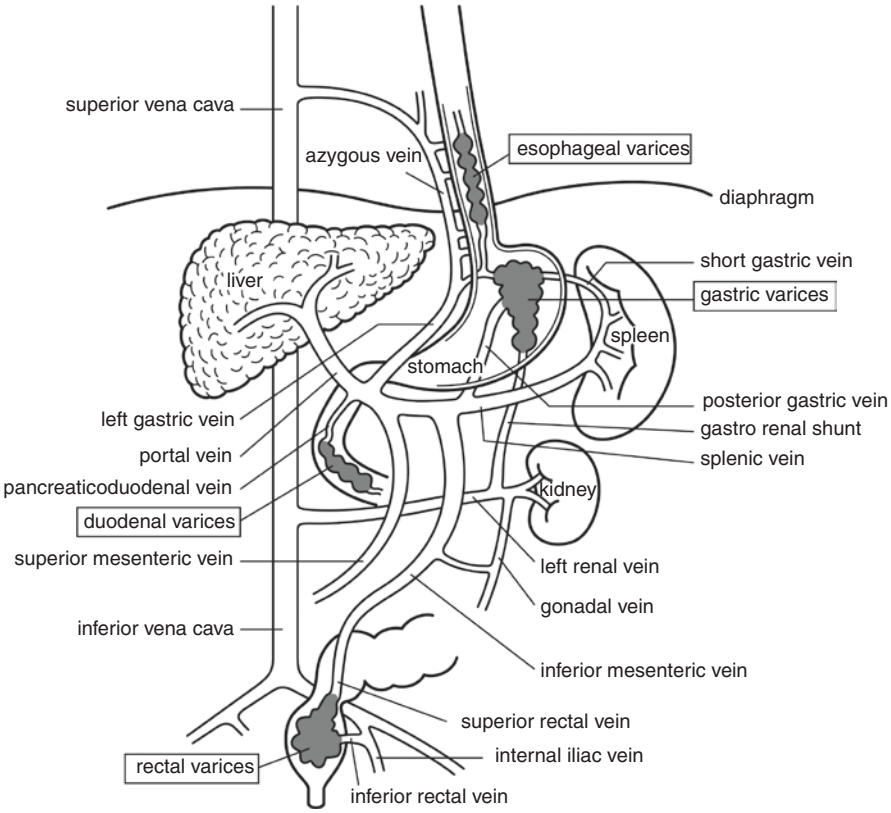


Fig. 8.5 Schema of gastrointestinal varices and collateral hemodynamics in portal hypertension. Gastric varices are fed by the left, short, and posterior gastric vein. The blood then flows into the gastrorenal shunt. Duodenal varices are fed by the superior and inferior pancreaticoduodenal veins. The blood then flows into the left renal vein or IVC through the gonadal vein. Rectal varices form in the superior rectal vein, a branch of IMV. The blood flows from rectal varices into the inferior rectal vein and the internal iliac vein

The hemodynamics are unknown in about a half of rectal varices. In general, the superior rectal vein branching out of the inferior mesenteric vein serves as the feeding vessel to rectal varices. After a rectal varix forms, the blood flows into the internal iliac vein through the middle and inferior rectal veins.

8.6 Bleeding

Once bleeding starts in an ectopic varix, it is often fatal because the blood flow rate and volume are high. Ectopic varices are generally found after gastrointestinal bleeding. Forty-five percent of ectopic varices are hemorrhagic [7]. While bleeding

is most frequent in rectal and duodenal varices, the rate of bleeding is the highest in small intestinal varices followed by duodenal and rectal varices. Bleeding recurs in ectopic varices in colonic stoma. The rate of bleeding is from 3 to 5% [30]. In Japan, the reported rate of bleeding is over 30% in rectal varices [11]. However, the frequency of bleeding is low in other countries: four of 112 patients (3.6%) according to McCormack et al. and two of 100 patients (2%) according to Hosking et al. [31, 32]. Frequent bleeding is therefore considered unlikely.

8.7 Conclusion

Ectopic varices have been the main topic at a number of gastroenterological conferences and remain an important subject associated with portal hypertension. As the treatment of esophageal and gastric varices is standardized, ectopic varices may further increase with their spread. The pathophysiology of ectopic varices should be elucidated to establish a means of diagnosis and treatment.

References

1. Bosch J, Pizcueta P, Feu F, Fernández M, García-Pagán JC. Pathophysiology of portal hypertension. Gastroenterol Clin N Am. 1992;21:1–14.
2. Buob S, Johnston AN, Webster CR. Portal hypertension: pathophysiology, diagnosis, and treatment. J Vet Intern Med. 2011;25:169–86. https://doi.org/10.1111/j.1939-1676.2011.00691.x.
3. Kinkhabwala M, Mousavi A, Iyer S, Adamsons R. Bleeding ileal varicosity demonstrated by transhepatic portography. Am J Roentgenol. 1977;129:514–6.
4. Norton ID, Andrews JC, Kamath PS. Management of ectopic varices. Hepatology. 1998;28:1154–8.
5. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46:922–38.
6. Kumagai Y, Makuuchi H, Oomori Y. Rare gastrointestinal varices. In: Ideduki Y, editor. Tokyo: Tokyo Igakusha; 1995. p. 9–133. (In Japanese).
7. Watanabe N, Toyonaga A, Kojima S, Takashimizu S, Oho K, Kokubu S, et al. Current status of ectopic varices in Japan: results of a survey by the Japan Society for Portal Hypertension. Hepatol Res. 2010;40:763–76. https://doi.org/10.1111/j.1872-034X.2010.00690.x.
8. Lebrec D, Benhamou JP. Ectopic varices in portal hypertension. Clin Gastroenterol. 1985;14:105–21.
9. Alberti W. Uber den rontogenologischen Nachweis von Varizen im Bulbus duodeni. Hortsh Roengestr. 1931;43:63–5.
10. Case records of the Massachusetts General Hospital, case 40102. N Engl J Med. 1954;250:434.
11. Shudo R, Yazaki Y, Sakurai S, Uenishi H, Yamada H, Sugawara K. Clinical study comparing bleeding and nonbleeding rectal varices. Endoscopy. 2002;34:189–94.
12. Rabinovitz M, Schade RR, Dindzans VJ, Belle SH, Van Thiel DH, Gavaler JS. Colonic disease in cirrhosis. An endoscopic evaluation in 412 patients. Gastroenterology. 1990;99:195–9.
13. Chawla Y, Dilawari JB. Anorectal varices-their frequency in cirrhotic and non-cirrhotic portal hypertension. Gut. 1991;32:309–11.

14. Sauerbruch T, Weinzierl M, Dietrich HP, Antes G, Eisenburg J, Paumgartner G. Sclerotherapy of a bleeding duodenal varix. Endoscopy. 1982;14:187–9.
15. Foutch PG, Sivak MV Jr. Colonic variceal hemorrhage after endoscopic injection sclerosis of esophageal varices: a report of three cases. Am J Gastroenterol. 1984;79:756–60.
16. Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc. 2010;22:1–9. https://doi.org/10.1111/j.1443-1661.2009.00929.x.
17. Matsui S, Kudo M, Ichikawa T, Okada M, Miyabe Y. The clinical characteristics, endoscopic treatment, and prognosis for patients presenting with duodenal varices. Hepatogastroenterology. 2008;55(84):959–62.
18. Khouqeer F, Morrow C, Jordan P. Duodenal varices as a cause of massive upper gastrointestinal bleeding. Surgery. 1987;102:548–52.
19. Dhiman RK, Choudhuri G, Saraswat VA, Mukhopadhyay DK, Khan EM, Pandey R, et al. Endoscopic ultrasonographic evaluation of the rectum in cirrhotic portal hypertension. Gastrointest Endosc. 1993;39:635–40.
20. Nishida N, Sakai G, Morimoto A, Isota M, Kaminou T, Matsuoka T, et al. Gadolinium enhanced three-dimensional magnetic resonance portography with subtraction. Br J Radiol. 2001;74:147–52.
21. Fukuhara T, Kakizawa H, Aikata H, Tani C, Ishikawa M, Awai K, et al. Usefulness of multidetector row computed tomography for management of duodenal varices by emergency balloon-occluded retrograde transvenous obliteration. Clin J Gastroenterol. 2013;6:243–7. https://doi.org/10.1007/s12328-013-0379-9.
22. Arora A, Rajesh S, Meenakshi YS, Sureka B, Bansal K, Sarin SK. Spectrum of hepatofugal collateral pathways in portal hypertension: an illustrated radiological review. Insights Imaging. 2015;6(5):559–72. https://doi.org/10.1007/s13244-015-0419-8.
23. Burroughs AK, Groszmann R, Bosch J, Grace N, Garcia-Tsao G, Patch D, et al. Assessment of therapeutic benefit of antiviral therapy in chronic hepatitis C: is hepatic venous pressure gradient a better end point? Gut. 2002;50:425–7. https://doi.org/10.1136/gut.50.3.425. PMID:11839726.
24. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology. 2007;133:481–8. https://doi.org/10.1053/j.gastro.2007.05.024. PMID: 17681169.
25. Haruta I, Isobe Y, Ueno E, Toda J, Mitsunaga A, Noguchi S, et al. Balloon-occluded retrograde transvenous obliteration (BRTO), a promising nonsurgical therapy for ectopic varices: a case report of successful treatment of duodenal varices by BRTO. Am J Gastroenterol. 1996;91:2594–7.
26. Jonnalagadda SS, Quiason S, Smith OJ. Successful therapy of bleeding duodenal varices by TIPS after failure of sclerotherapy. Am J Gastroenterol. 1998;93:272–4.
27. Saad WE, Lippert A, Saad NE, Caldwell S. Ectopic varices: anatomical classification, hemodynamic classification, and hemodynamic-based management. Tech Vasc Interv Radiol. 2013;16:158–75. https://doi.org/10.1053/j.tvir.2013.0.2.004.
28. Sato T. Treatment of ectopic varices with portal hypertension. World J Hepatol. 2015;7:1601–5. https://doi.org/10.4254/wjh.v7.i12.1601.
29. Itzchak Y, Glickman MG. Duodenal varices in extrahepatic portal obstruction. Radiology. 1977;124:619–24.
30. Wang L, Zhou JL, Yang N, Zhang GN, Lu JY, Xiao Y, et al. Ectopic variceal bleeding from colonic stoma: two case reports. Medicine (Baltimore). 2015;94:e406. https://doi.org/10.1097/MD.0000000000000406.
31. McCormack TT, Bailey HR, Simms JM, Johnson AG. Rectal varices are not piles. Br J Surg. 1984;71:163.
32. Hosking SW, Smart HL, Johnson AG, Triger DR. Anorectal varices, haemorrhoids, and portal hypertension. Lancet. 1989;1(8634):349–52.

Chapter 9
The Role of Endoscopic Ultrasonography for Esophagogastric Varices

Atsushi Irisawa, Goro Shibukawa, Ai Sato, and Akane Yamabe

Abstract In patients with esophageal varices accompanied by complicating portal hypertension, a large network of portal-systemic collateral veins develops. Endoscopic ultrasonography (EUS), especially ultrasound mini-probe, allows for noninvasive imaging of collateral circulation in the esophagus as well as the inside and outside of the gastric wall and allows treatment selection tailored to the hemodynamics of each individual varix. The characteristics to be evaluated in a patient with esophagogastric varices with EUS include the following: (1) diameter of the varix, (2) perforating veins, (3) periesophageal veins/perigastric veins, and (4) paraesophageal veins/paragastric veins. The observation of these structures provides important information for safer and more effective treatments; in addition, EUS also provides information that is useful for the prediction of recurrence.

Keywords EUS · Esophageal varices · Gastric varices

9.1 Introduction

In patients with esophageal varices accompanied by complicating portal hypertension, a large network of portal-systemic collateral veins develops. Frequent and significant pathways of collaterals consist of gastroesophageal varices and veins outside the esophageal/gastric wall extending from the left and short gastric veins [1–4]. Therefore, in the treatment of esophagogastric varices, understanding the morphology of esophagogastric varices, the local hemodynamics of varices, and portal hemodynamics is extremely important for the safety and efficacy of treatment.

A. Irisawa (✉) · G. Shibukawa · A. Sato · A. Yamabe
Department of Gastroenterology, Aizu Medical Center, Fukushima Medical University, Aizuwakamatsu, Japan
e-mail: irisawa@fmu.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_9

Endoscopic ultrasonography (EUS) allows for noninvasive imaging of collateral circulation in the esophagus as well as the inside and outside of the gastric wall and allows treatment selection tailored to the hemodynamics of each individual varix [5–8]. In addition to this, in the posttreatment determination of treatment efficacy, EUS also provides information for determination of whether a complete recovery will be achieved by the treatment or whether additional treatment is necessary [9]. In this chapter, we explain the use of EUS for diagnosing esophagogastric varices and demonstrate the effective application of EUS before and after treatment.

9.2 EUS Divides and Methods

9.2.1 EUS Devices

The types of EUS that are used in the diagnosis of esophagogastric varices can be roughly classified into two major categories. The first one includes devices for exclusive use in endoscopic ultrasonography such as radial scanning EUS and linear scanning EUS. The second category includes the ultrasound mini-probe (UMP). UMP (20 MHz) is suitable for use in the determination of the local hemodynamics of esophagogastric varices; in particular, detailed observation using a UMP is required when to monitor esophageal varices [2]. On the other hand, devices for exclusive use with EUS are used in the assessment of blood vessels outside the gastric wall as well as the inflow circuit, features that cannot be evaluated with UMP because of an attenuation of the ultrasonic beam. Furthermore, the latest devices for exclusive use in electronic scan-type EUS have a color Doppler function, allowing assessment of the blood flow direction and blood flow rate in the perforating veins (Pv) of the esophagus and gastric wall [10]. For pre- and posttreatment evaluations, observations using UMP are sufficient. In this chapter, the images of UMP are mainly described.

9.2.2 Observation of Esophageal Varices

When a UMP is used, a cap with water supply function is attached to the accessory channel of the endoscope, and observations are carried out while the esophageal lumen is filled with degassed water using the water supply function. Specifically, the stomach is filled by injection with approximately 400 mL of degassed water; the air in the gastric fundus is suctioned, while degassed water is being sent into the esophagus, and then the UMP is inserted and observation is carried out (Fig. 9.1). The basic scanning method is as follows: the UMP is pulled out directly from under the cardia (the UMP is pulled out to approximately 20 mm from the tip of the scope, and then each scope is pulled out) as simultaneous observations are carried out. During endoscopic examination using a water supply function, users must keep in mind that the strong water flow may cause the formation of air bubbles, which may

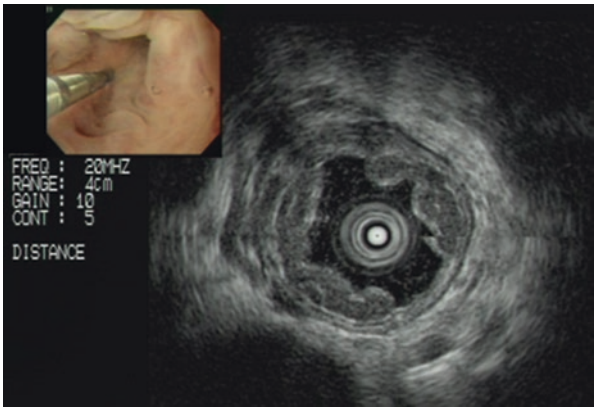


Fig. 9.1 The observation of esophageal varices using UMP. During UMP manipulation, degassed water is continuously supplied to fill in the esophageal lumen to obtain the clear image of UMP

interfere with the observation. The same procedure is utilized when we work with devices for exclusive use with EUS, but caution is required not to crush varices by insufflation of the tip-mounted balloon.

9.2.3 Observation of Gastric Varices

To observe gastric varices, first approximately 300–500 mL of degassed water is used to fill the stomach lumen, and ultrasonographic observation is carried out while the device is immersed in the water. This applies to devices both for exclusive use with EUS and UMP. When UMP is used, all of the gastric varices can be regularly observed without difficulty through inverted scanning under direct endoscopy, but fundamentally, with EUS devices, observations are carried out by looking down, and for that reason, it is difficult to determine whether all varices have been observed or not. On the other hand, when observing blood vessels outside the gastric wall, assessments using UMP can be difficult because of attenuation.

9.3 Diagnosis of Esophagogastric Varices by Endoscopic Ultrasonography

According to the Japanese clinical guidelines for the management of portal hypertension (third edition) [11], the characteristics to be evaluated in a patient with esophagogastric varices with EUS include the following: (1) diameter of the varix, (2) Pv, (3) periesophageal veins/perigastric veins, and (4) paraesophageal/gastric veins. The following section describes observation methods focused on the aforementioned items, as well as their clinical significance. Additionally, the methods indicated in the guidelines are shown in Table 9.1.

Table 9.1 General rules for recording EUS findings of esophagogastric varices (modified from "The general rules for study of portal hypertension, Third Edition" [11])

General rules for recording EUS findings of esophagogastric varices
1. Diameter [*D*]
Describe the maximum shoort-axis diameter (mm) of varix
D(0) is used for those that do not have a luminal image after treatment
2. Perforating veins [Pv]
Presence/absence is indicated by (+) (−), and if it is present, the maximum diameter (mm) is added
3. Periesophageal/gastric vein [Peri-v]
Presence/absence is indicated by (+) (−)
4. Paraesophageal/gastric vein [Para-v]
Presence/absence is indicated by (+) (−)

9.3.1 Esophageal Varices

9.3.1.1 Local Endoscopic Ultrasonographic Analysis of Esophageal Varices

There is a considerable variation in the development of collateral circulation resulting from portal hypertension, but from the perspective of the development of collateral circulation based on existing vascular networks, the basic hemodynamics are generally predetermined [2, 12]. Figure 9.2 shows collateral circulation found inside and outside the esophageal wall through observation using EUS (particularly UMP). In every case, the degree of development of each blood vessel should be evaluated on the basis of this figure. In addition, the resulting EUS images allow for estimation of the efficacy of endoscopic varicealography during injection sclerotherapy (EVIS) and are useful for the selection of the proper endoscopic treatment (endoscopic injection sclerotherapy [EIS] or endoscopic variceal ligation [EVL]) (the selection criteria will be described in detail later).

9.3.1.2 Morphology of Esophageal Varices

In the observation of the morphology of esophageal varices, the two important factors are diameter and internal morphology. Esophageal varices are present mainly in the submucosal layer and are observed as images of the hypoechoic lumen. Their morphology can be classified into two types: that with an oval or elliptic shape observed as a single isolated blood vessel (solitary type, Fig. 9.3a) and that made of thin varices stacked upon each other (reticular type, Fig. 9.3b). The reticular type usually requires a larger quantity of sclerosing agents and more frequent treatment sessions than the solitary type. In addition, appropriate selection of puncture needle (diameter and length) depending on the morphology and diameter is important for proper treatment.

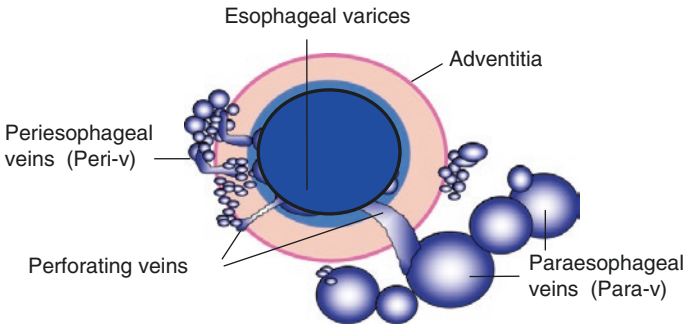


Fig. 9.2 The schema of the UMP image inside and outside esophageal wall (Modified from Irisawa et al. [6])

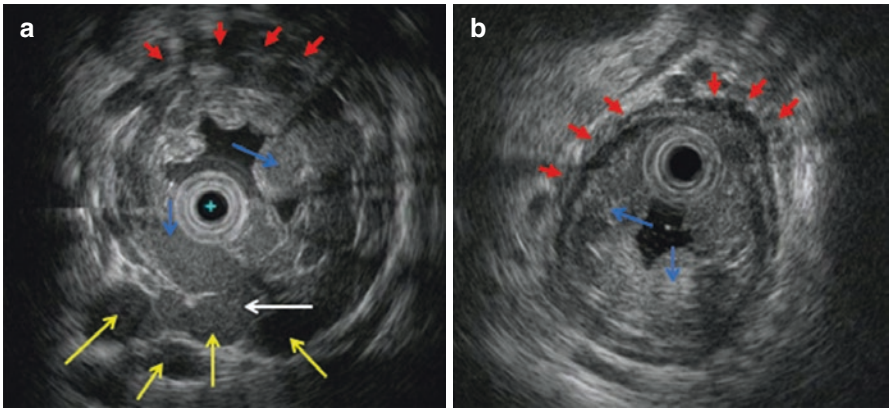


Fig. 9.3 (**a**) Solitary-type esophageal varices were seen (*blue arrows*). In addition, periesophageal veins (*red arrows*), paraesophageal veins (*yellow arrows*), and the perforating vein between esophageal varix and paraesophageal vein (*white arrow*) were identified. (**b**) Reticular-type esophageal varices were seen (*blue arrows*). In addition, periesophageal veins (*red arrows*) were identified. Due to the existence of periesophageal veins, the esophageal adventitia becomes "shaggy," and observation may show the outer longitudinal muscle layer as even more hypoechoic

After treatment, the presence or absence of residual lumen in the esophageal wall should be checked, or when consolidation therapy is performed, the thickening of the esophageal wall should be checked (Fig. 9.4). The risk of recurrence is extremely low if a uniform wall thickening without a luminal structure is observed.

9.3.1.3 Perforating Veins (Pv) of the Esophageal Wall

Pv of the esophageal wall are blood vessels that communicate with varices in the esophageal wall and blood vessels outside the esophageal wall. Such Pv can be observed relatively easily with UMP (Fig. 9.3a). Studies using color Doppler EUS have shown that most Pv serve as inflow paths (Fig. 9.5); therefore, in a sense, Pv also serve as variceal inflow vessels from the side of the esophagus [5, 13].

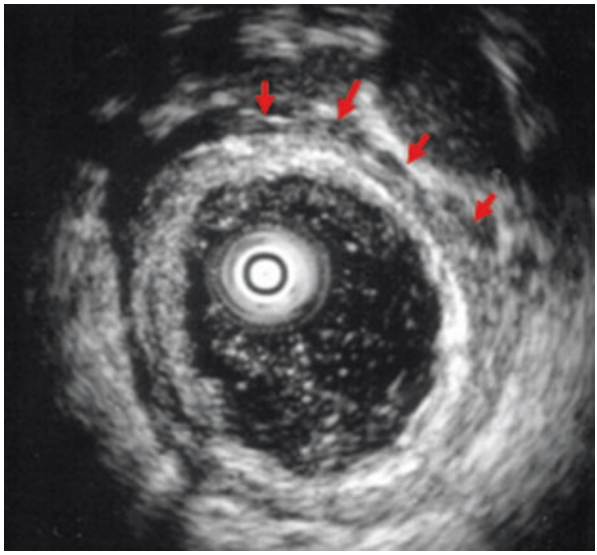


Fig. 9.4 UMP image after treatment (sclerotherapy). Wall thickness without esophageal varices was seen; however, remaining periesophageal veins (*red arrow*) were seen. This finding indicates the high risk of recurrence after treatment

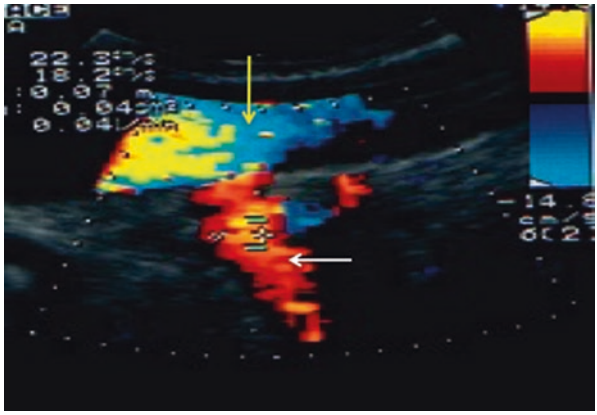


Fig. 9.5 Color Doppler EUS showed that the perforating veins (*white arrow*) served as inflow paths to the esophageal varix (*yellow arrow*)

In the actual delivery of treatment, the significance of the observation of Pv has two aspects. The first is that they serve as an outflow path for sclerosant during sclerotherapy, and the second is that if residual Pv remain present after treatment, they can serve as variceal inflow vessels for recurrent varices [14].

(a) Outflow pathway of the sclerosant
With EIS, variceal inflow vessels need to be embolized completely through intravascular injection of 5% ethanolamine oleate (EO), but in patients with large Pv, the injected EO can leak into the general circulation through the Pv (esophageal extramural shunt), and for this reason, the variceal inflow vessels should not be embolized in this situation (Fig. 9.6). In addition, the leaked EO is also likely to cause various complications, such as hemolysis, renal failure,

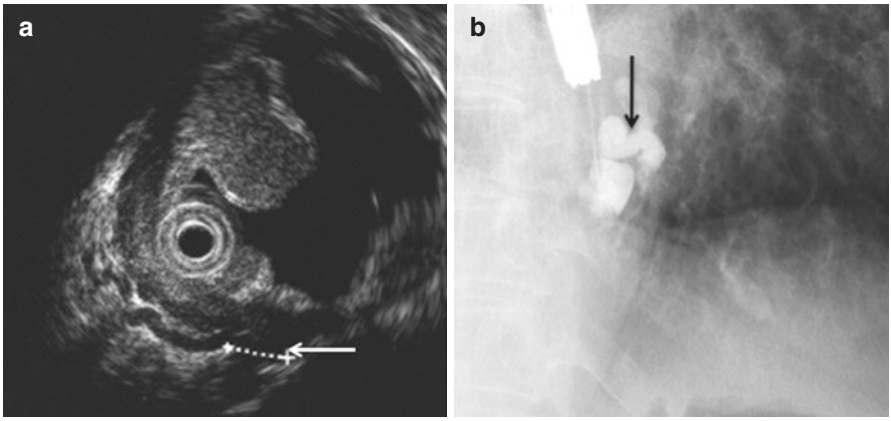


Fig. 9.6 (**a**) UMP showed a large perforating vein (*white arrow*) between esophageal varix and para-esphageal vein. (**b**) Endoscopic varicealography during injection sclerotherapy showed that sclerosant with contrast medium did not come into the feeding vein due to flow-out of injected sclerosant through the perforating vein (*black arrow*)

and heart failure. Conducting observations using EUS and determining the presence of Pv as well as their diameters before treatment are useful to ensure safe and effective treatment.

(b) Inflow circuit of recurrent varices
When sclerotherapy using the intravascular injection method is performed, endothelial cells in the Pv are also at risk of being damaged by the EO, and in most cases, those Pv are embolized as well. On the other hand, with the EVL method, the Pv are not necessarily ligated and often remain present. If EUS observations after treatment reveal the presence of residual Pv, the risk of recurrence is high and, therefore, additional treatments such as consolidation therapy should also be taken into consideration [10].

9.3.1.4 Extramural Vessels of the Esophagus

The venous systems that can be observed outside the esophageal wall include the paraesophageal venous system and the azygos vein system. The paraesophageal venous system can be observed as it is subdivided into two categories depending on their location around the esophageal wall: the periesophageal veins (Peri-v, Fig. 9.3) and the paraesophageal veins (Para-v, Fig. 9.3) [2, 7]. Peri-v are a group of blood vessels that are in contact with the esophageal adventitia or which partially penetrate the muscularis of the esophageal wall (in many cases, the esophageal adventitia becomes “shaggy” and observation may show the outer longitudinal muscle layer as even more hypoechoic). Para-v are a group of slightly larger blood vessels that are present separately from the esophageal adventitia.

(a) Periesophageal veins (Peri-v)
Previous studies have shown Peri-v to be involved in the development of esophageal varices as well as in their recurrence after treatment [10]. At the time of the initial treatment, the complete disappearance of Peri-v is important for the treatment to be effective. If the development of Peri-v is confirmed before treatment, EO needs to be injected until EVIS findings show a group of thin blood vessels around the esophageal varices. In other words, in the treatment of varices with hemodynamics with developed Peri-v, the risk of recurrence is believed to be higher with EVL because it is less likely to affect extramural blood vessels; therefore, EIS using intravascular injection should be selected if possible. In addition, if EUS observation after treatment reveals the presence of Peri-v, the possibility of relapse may be high, and close follow-up needs to be carried out [10].

(b) Paraesophageal veins (Para-v)
While previous reports have shown that massive development of Para-v was associated with low risk of variceal recurrence, other reports have stated that Para-v were closely related to recurrence because they acted as variceal inflow vessels for Pv; therefore, no consensus has yet been reached whether or not to eradicate Para-v [10]. However, if Para-v develop in the absence of Pv, they may act as collateral circulation to reduce the portal blood pressure after treatment of esophageal varices [8]. From this perspective, cases with EUS showing no Pv and with noticeable Para-v are good indications for EVL [5].

9.3.2 Gastric Varices

9.3.2.1 Local EUS Analysis of Gastric Varices

Gastric varices are depicted as echo-free images of lumens inside the third layer (submucosal layer) of the gastric wall. With EUS especially, the outer layer of gastric varices can be depicted as thinner than the superficial layer of healthy gastric mucosa, indicating that erosive changes at the surface were a risk factor for a rupture of gastric varices. Figures 9.7 and 9.8 (schema and real images) show collateral circulation inside and outside the gastric wall as observed using EUS.

9.3.2.2 Morphology of Gastric Varices (Diameter of Varix)

Even if some varices seem extremely large under endoscopic observation, all varices do not necessarily consist entirely of thick varices. With UMP, the actual size of the gastric varices can be seen objectively. Previous report [15] has shown that the diameter of gastric varices is correlated with blood flow; thus, when performing EIS in gastric varices with a diameter of 5 mm or greater, cyanoacrylates are needed in order to control the voluminous blood flow. Also, after treatment, EUS is highly useful for confirming the complete disappearance of lumens representing the gastric varices. The rate of recurrence has been found to be high in cases showing residual

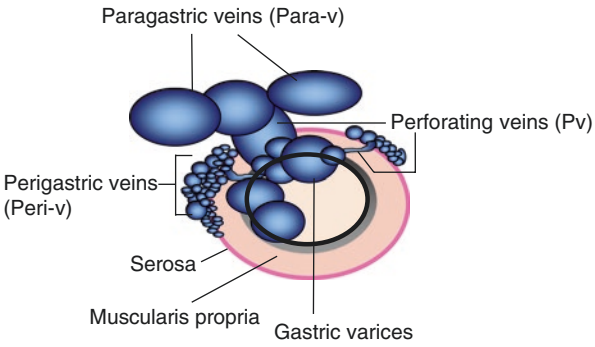


Fig. 9.7 The schema of the UMP image inside and outside gastric wall

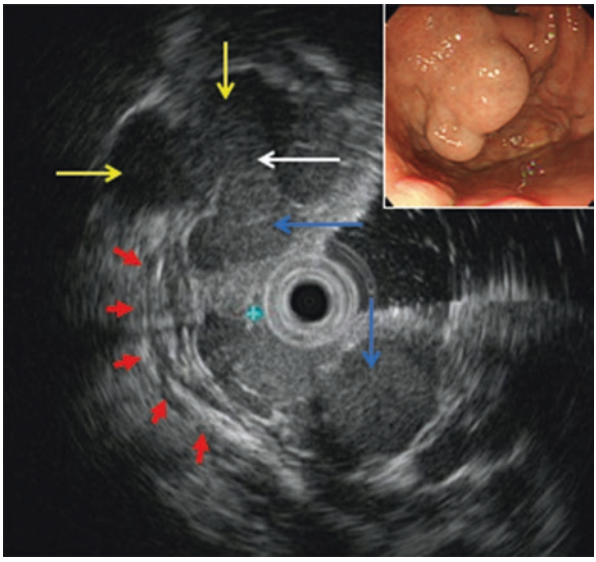


Fig. 9.8 Gastric varices were seen (*blue arrows*). In addition, periesophageal veins (*red arrows*), paraesophageal veins (*yellow arrows*), and the perforating vein between gastric varix and paraesophageal vein (*white arrow*) were identified

lumen; thus, EUS also provides information that is useful for the determination of the need for additional treatment. Wakatsuki et al. [16] reported recommended concentration of cyanoacrylate (alpha-cyanoacrylate monomer) to be injected according to the EUS findings; if the minor axis of gastric varices by EUS is identified as smaller than 10 mm, 62.5% cyanoacrylate is recommended; if it is identified as 10 mm or over, 75% cyanoacrylate is recommended to prevent leakage of cyanoacrylate from gastric varices to general circulation via gastrorenal shunt [17]. After cyanoacrylate injection, UMP can evaluate whether variceal lumens were completely eradicated or not (Fig. 9.9).

9.3.2.3 Perforating Veins [Pv] of the Gastric Wall

Through identification of gastric wall Pv communicating with gastric varices and gastric extramural blood vessels, observation of the deeper layers allows for the

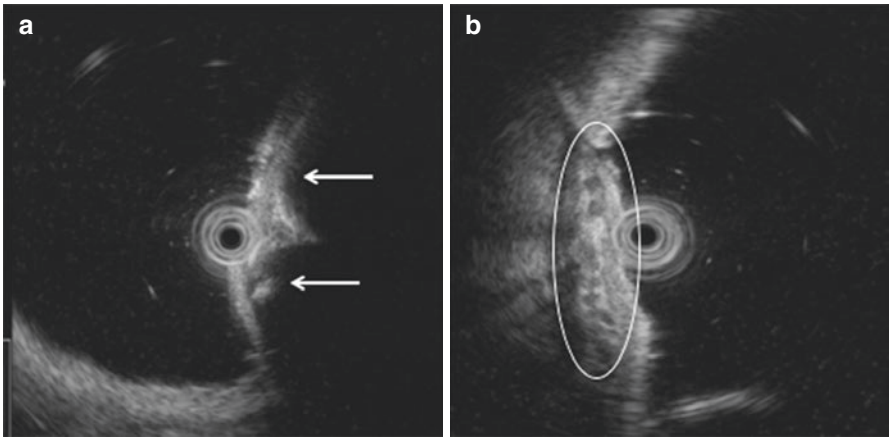


Fig. 9.9 (**a**) UMP image after cyanoacrylate injection. UMP showed hyperechoic layers with acoustic shadow (*white arrow*). Gastric varices were completely obliterated. (**b**) UMP revealed the remaining small varices in the gastric wall (*oval line*) after treatment

estimation of the presence or absence of variceal inflow vessels or the presence of a shunt between the portal vein and systemic circulation (gastrorenal shunt). However, such an assessment requires an observation using devices for exclusive use in EUS. In addition, the injected cyanoacrylate has been thought to be at risk of leaking into the systemic circulation when the diameters of the Pv are large; therefore, this observation is also important to avoid procedure-related adverse effect [18]. Of note is that the presence of residual Pv after treatment has been thought to be involved in recurrence.

9.3.2.4 Extramural Blood Vessels of the Gastric Wall

The blood vessels outside the gastric wall can be classified into two categories, namely, the Peri-v that are groups of small blood vessels in contact with the gastric serosa or that in some cases penetrate the muscularis of the gastric wall and the Para-v that are slightly larger in size and are located away from the gastric wall [7]. The clinical significance of evaluating Peri-v and Para-v before treatment remains undetermined. However, the presence of residual Pv and Peri-v communicating with Para-v has been shown to be involved in recurrence. In the same way as in the case of the esophagus, confirmation of the presence of those groups of blood vessels during EUS observation suggests that consolidation therapy should be performed in order to prevent recurrences.

9.3.2.5 Relationship with Esophageal Varices

The continuity between the lumen of gastric varices and esophageal varices can be confirmed using EUS. In other words, EUS allows for diagnosing whether gastric

varices are solitary or not. If the findings suggest a continuity, it can be predicted that the gastric varices can be properly treated by injection of a sclerosant from the esophageal side of the varices.

9.4 Conclusion

Esophagogastric varices can be treated even without performing EUS. However, performing EUS before and after treatment allows the treatment to be safer and more effective; in addition, EUS also provides information that is useful for the prediction of recurrence. EUS is an essential tool for optimal treatment and management of esophagogastric varices.

References

1. Widrich WC, Srinivasan M, Semine C, et al. Collateral pathways of the left gastric vein in portal hypertension. Am J Roentgenol. 1984;142:375–82.
2. Bengmark S, Borjesson B, Hoevels J, et al. Obliteration of esophageal varices by PTP. Ann Surg. 1979;190:549–54.
3. Hashizume M, Kitano S, Sugimachi K, et al. Three- dimensional view of the vascular structure of the lower esophagus in clinical portal hypertension. Hepatology. 1988;8:1482–7.
4. Frederick HM, Clements JL, Colvin RS. Retrocardiac densities due to paraesophageal varices: roentgenographic detection. South Med J. 1985;78:1371–2.
5. Caletti GC, Brocchi E, Ferrari A, et al. Value of endoscopic ultrasonography in the management of portal hypertension. Endoscopy. 1992;24:342–6.
6. Irisawa A, Obara K, Sato Y, et al. An endoscopic analysis of collateral veins inside and outside the esophageal wall in portal hypertension. Gastrointest Endosc. 1999;50:374–80.
7. Kassem MA, Salama AZ, Rosch T. Endoscopic ultrasonography in portal hypertension. Endoscopy. 1997;29:399–406.
8. Irisawa A, Shibukawa G, Obara K, et al. Collateral vessels around the esophageal wall in patients with portal hypertension: comparison of EUS imaging and microscopic findings at autopsy. Gastrointest Endosc. 2002;56:249–53.
9. Nakamura S, Murata Y, Mitsunaga A, et al. Hemodynamics of esophageal varices on three-dimensional endoscopic ultrasonography and indication of endoscopic variceal ligation. Dig Endosc. 2003;15:289–97.
10. Sato T, Yamazaki K, Toyota J, et al. Clinical experience with newer electronic radial-type endoscopic color Doppler ultrasonography in the diagnosis of esophageal varices. J Med Ultrason 2001. 2010;37:117–21.
11. The general rules for study of portal hypertension. 3rd ed. Kanehara-Shuppan: The Japanese Society for Portal Hypertension; 2013. p. 41–2.
12. Irisawa A, Obara K, Bhutani M, et al. Role of para-esophageal collateral veins in patients with portal hypertension based on the results of endoscopic ultrasonography and liver scintigraphy analysis. J Gastroenterol Hepatol. 2003;18:309–14.
13. Sato T, Higashino K, Toyota J, et al. The usefulness of endoscopic color Doppler ultrasonography in the detection of perforating veins of esophageal varices. Dig Endosc. 1996;8:180–3.
14. Irisawa A, Saito A, Obara K, et al. Endoscopic recurrence of esophageal varices is associated with the specific EUS abnormalities: severe periesophageal collateral veins and large perforating veins. Gastrointest Endosc. 2001;53:77–84.

15. Imamura H, Irisawa A, Shibukawa G, et al. Echo-endoscopic analysis of variceal hemodynamics in patient with isolated gastric varices. Endosc Ultrasound. 2014;3:238–44.
16. Wakatsuki T, Obara K, Irisawa A, et al. Analysis of prognostic factors in patient with gastric varices after endoscopic treatment. Dig Endosc. 2009;21:232–8.
17. Irisawa A, Obara K, Sato Y, et al. Adherence of cyanoacrylate which leaked from gastric varices to the left renal vein during injection sclerotherapy: a histopathologic study. Endoscopy. 2000;32:804–6.
18. Bhatia V. Endoscopic ultrasound (EUS) for esophageal and gastric varices: how can it improve the outcomes and reduce complications of glue injection. J Clin Exp Hepatol. 2012;2:70–4.

Chapter 10
Contrast-Enhanced Ultrasound of Liver Cirrhosis

Yasukiyo Sumino

Abstract For taking care of patients with liver disease, it is important to understand both the liver histology and the liver test data. Liver biopsy is the most reliable way (gold standard) to know the histology, but invasive. It is also well accepted that the peripheral blood flow within the liver parenchyma is easily influenced by histological changes, such as liver fibrosis, necrosis, edema, and collapse. On the other hand, the liver function is regulated by four main factors, uptake, metabolism, secretion of the liver cells, and liver blood flow. Therefore, analyzing the hemodynamics in the peripheral area of the liver parenchyma may become a relevant way for estimating the histology and the function of the liver. Accordingly, we have studied the significance of the arrival-time parametric image and the perfusion parametric image obtained by Sonazoid®-enhanced ultrasound in diagnosing hepatitis C virus-related chronic liver diseases, especially liver cirrhosis.

As a result, we found analyzing the hepatic microcirculation and the portal vein blood flow by contrast-enhanced ultrasound may be of great help for understanding what is happening within the liver parenchyma in patients with liver cirrhosis.

Keywords Contrast-enhanced ultrasound · Liver cirrhosis · Liver perfusion · Liver hemodynamics

10.1 Introduction

The liver receives its blood supply via two distinct circulatory routes: the hepatic artery and the portal vein. It is well known that major changes in the hemodynamics of these circulatory routes occur when chronic liver disease progresses to liver

Y. Sumino
Department of Gastroenterology and Hepatology, Toho University Omori Medical Center, Tokyo, Japan
e-mail: sumino@med.toho-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_10

cirrhosis. In the healthy liver, the hepatic artery supplies the bile duct, and the portal vein provides most of the sinusoidal blood flow and also supplies the liver parenchyma. According to Reuter and Redman [1], these hemodynamics are maintained until the onset of chronic hepatitis, but once the disease has progressed to liver cirrhosis, blood flow into the sinusoids from the portal vein is reduced and compensated by arterial blood. As liver cirrhosis progresses, over half of the blood flowing into the sinusoids is arterial blood, and in the terminal phase retrograde flow of arterial blood joins the portal vein via the sinusoids. This is known as hepatic arterial dominance. Although there have been various theories regarding this mechanism, Lautt et al. reported the role of adenosine in the control of hepatic flow [2]. These hemodynamic changes in the hepatic parenchyma provide important information for the treatment of liver cirrhosis, but to date, no optimal method for obtaining this information has been introduced in clinical settings. However, the use of Sonazoid®, an ultrasound contrast agent, facilitates investigation of hepatic parenchymal hemodynamics at an appreciable level of detail. We introduce it here because it has already been successfully employed at our hospital as an important tool for disease state analysis during the treatment of liver cirrhosis.

10.2 Methods

10.2.1 Contrast-Enhanced Ultrasound

First, we demonstrate the actual opacification that occurs during Sonazoid® contrast-enhanced ultrasound (CEUS) imaging (Fig. 10.1).

Kidney
Sonazoid® is usually administered by intravenous bolus injection into a peripheral blood vessel. When injected into the cubital vein, it flows into the renal artery and immediately fills the renal parenchyma, causing opacification. This is a classic example of the opacification of organs that are supplied only by arteries.

Healthy liver
A Sonazoid® bolus injection first reaches the branches of the hepatic artery present in the hepatic parenchyma, but bubbles inside these arteries are extensively scattered throughout the hepatic parenchyma. After further 3–5 s, the bubbles that have passed through the gastrointestinal tract reach the intrahepatic portal vein branches and start contrast enhancement. Over time, the bubbles perfuse and fill the entire hepatic parenchyma. Several points are still unclear regarding the dynamics of Sonazoid® and the detailed mechanism of these contrast-enhanced findings. However, based on an electron microscopic study of rat and mouse liver by Ota et al. [3], we surmise that after blood flows into the liver from the hepatic artery, it first supplies the biliary system and then drains via the portal system or into the sinusoids as venous blood. Consequently, Sonazoid® bubbles passing through the hepatic artery reach the sinusoids at virtually the same time as the bubbles that

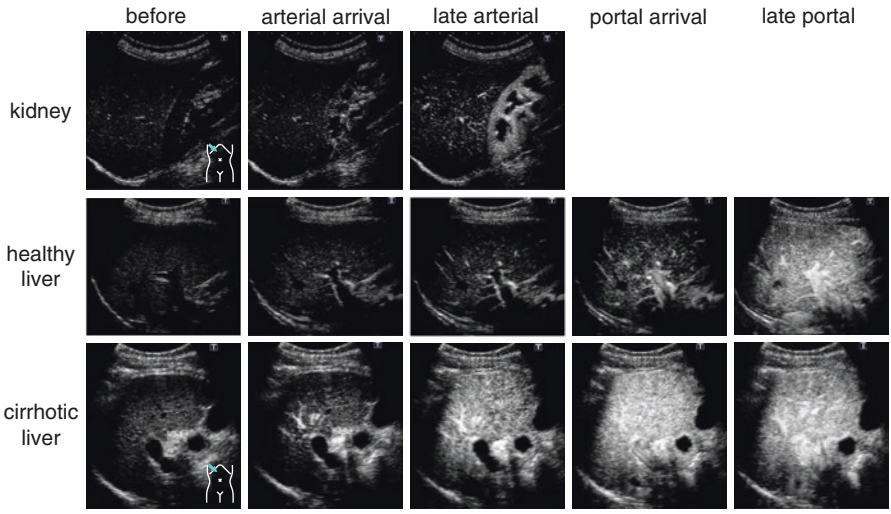


Fig. 10.1 Opacification occurring during Sonazoid® contrast-enhanced ultrasound in each organ. Kidney: Sonazoid® bubbles flow into the renal artery and immediately fill the renal parenchyma. Healthy liver: opacification occurs as follows: hepatic artery ⇒ portal vein ⇒ liver parenchyma. Cirrhotic liver: hepatic artery ⇒ liver parenchyma ⇒ portal vein (arterialization of the hepatic perfusion)

passed through the gastrointestinal tract and are added to the parenchymal perfusion. Thus, in a healthy liver, Sonazoid® bubbles (signifying blood flow) almost all perfuse the parenchyma during the portal venous phase. We generally refer to this as the portal perfusion pattern (P pattern). This is the basic pattern that is present in both the healthy and diseased liver (specifically chronic hepatitis), until the point at which stage F2 fibrosis occurs.

Liver cirrhosis

The pattern of the intravenous Sonazoid® bubbles first appears as opacification of the intrahepatic arterial branches and then the entire hepatic parenchyma. The bubbles still arrive in the portal vein after 3–5 s, but by this time, parenchymal perfusion has already reached the maximum. We believe this is caused by a mechanism that should compensate for the hypoperfusion of the portal venous circulation, which is caused by impeded blood flow into the liver due to liver cirrhosis. This mechanism involves opening of pathways for arterial blood to flow from the peripheral hepatic arteries directly into the small interlobular portal vein branches or into the sinusoids. We already know that "arterialization of the hepatic parenchymal perfusion occurs in cirrhotic patients," and we refer to this as arterialized perfusion (A pattern).

Thus, simply comparing healthy liver to cirrhotic liver demonstrates major differences in the hemodynamics, suggesting that Sonazoid® be capable of depicting this. To date, to further understand hepatic hemodynamics, we have used various methods in clinical settings including angiography, contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), and

perfusion scintigraphy [4–10]. However, the sensitivity and resolution of these methods are insufficient to fully examine the hepatic parenchymal microcirculation, and CEUS excels in this regard. Additionally, performing CEUS using Sonazoid® allows visual differentiation between hepatic arterial and venous dynamics, is minimally invasive, can be performed even if renal function is poor, has few effects on circulation because the injected dose is small, is tolerable to patients during injection, has very few side effects, and can be accomplished simply. These numerous advantages make this a highly beneficial test method, suited to clinical practice. The only issue with this investigation is that the opacification dynamics must be examined over time using moving images, which requires time and a playback device. During dynamic contrast-enhanced analysis, the use of a time-intensity curve is commonly considered to be beneficial, requires experience in order to become proficient at interpretation, and is difficult for the patient to understand. Hence, it might not be referred to as a representative method that is suitable for a clinical setting. Thus, the authors decided to use arrival-time parametric imaging (AtPI) [11] to obtain perfusion information equivalent to moving images even though the images produced are static. These images are easier to understand visually. This method can be easily explained before going into specific theories.

10.2.2 Arrival-Time Parametric Imaging (AtPI)

The authors used a technique developed by Kamiyama et al. [12] using a device called an Aplio XG (Aplio XG; Toshiba Medical Systems, Otawara, Japan), with a convex probe with a center frequency of 3.75 MHz. A bolus injection of Sonazoid® at the recommended dose (0.015 mL/kg) is administered into the cubital vein and flushed with 10 mL of physiological saline solution.

First, we performed AtPI. After Sonazoid® injection, each liver pixel is contrast enhanced by Sonazoid® bubbles, and the time when a certain luminance is achieved is defined at the arrival time for that pixel. Arrival time is divided into different time periods and color-coded. Particularly, the hepatic parenchyma is color-mapped with reference to the arrival time, and it is possible to discern immediately whether opacification is accelerated or delayed in each hepatic region using a single sheet of a completed static image (Fig. 10.2).

It is necessary to establish a time zero as a standard during color mapping. Generally, the time of injection of the contrast agent is considered as time zero, and the arrival time commonly refers to the period of time from time zero until the contrast agent arrives at the target organ. However, in order to analyze the changes in intrahepatic hemodynamics caused by intrahepatic lesions during the present study, we endeavored to eliminate the various effects affected by the lung and heart on the Sonazoid® bubbles injected into the cubital veins. For this reason, we defined the time when Sonazoid® arrives at the hepatic portal region via the hepatic artery as

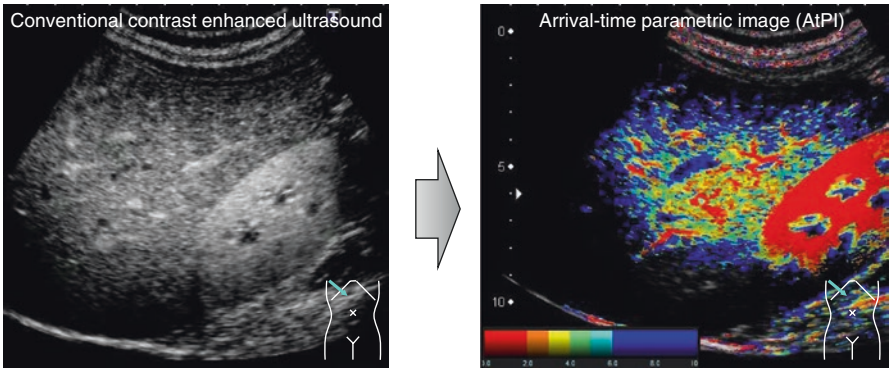


Fig. 10.2 Arrival-time parametric image: each liver pixel is contrast enhanced by Sonazoid bubbles, and the time when a certain luminance is achieved is defined at the arrival time for that pixel. Arrival time was divided according to different time periods and was color-coded. We use the renal parenchyma and define the time when 10% of the renal parenchyma in the region of interest (ROI) is contrasted as $t = 0$ (standard)

$t = 0$. Accordingly, color mapping during AtPI was performed using the difference in time between this zero point and the time at which Sonazoid® could be visualized in the hepatic parenchyma pixels. Furthermore, the narrow lumen of hepatic artery sometimes made it difficult to record stable images of the hepatic artery branches near the porta hepatis. Therefore, in such cases we used the renal parenchyma, which is opacified at approximately the same time as the hepatic artery [13] and define the time when 10% of the renal parenchyma in the region of interest (ROI) is contrasted as $t = 0$.

10.2.3 Perfusion Parametric Imaging (PPI)

Color mapping of the AtPI is further divided into two using the arrival time in the main trunk of the portal vein. Pixels that opacify faster than the arrival time are colored red, while pixels that arrive slower are colored blue, which is named perfusion parametric imaging (PPI). Red represents the pixels supplied with Sonazoid® bubbles by the arteries. Blue represents those pixels that were opacified later than the portal vein arrival time and, in principle, shows the opacification due to bubbles supplied via the portal vein. However, it is important to know that pixels will also appear blue if they arrive later than the portal vein arrival time in the peripheral hepatic circulation, even if the pixels were supplied by bubbles from arteries. We generally infer that red is more common, the pixels supplied via the arteries are more common, and it is clear that the hepatic parenchymal perfusion has undergone arterialization. When using this method, if the entire image is red, we refer to this as

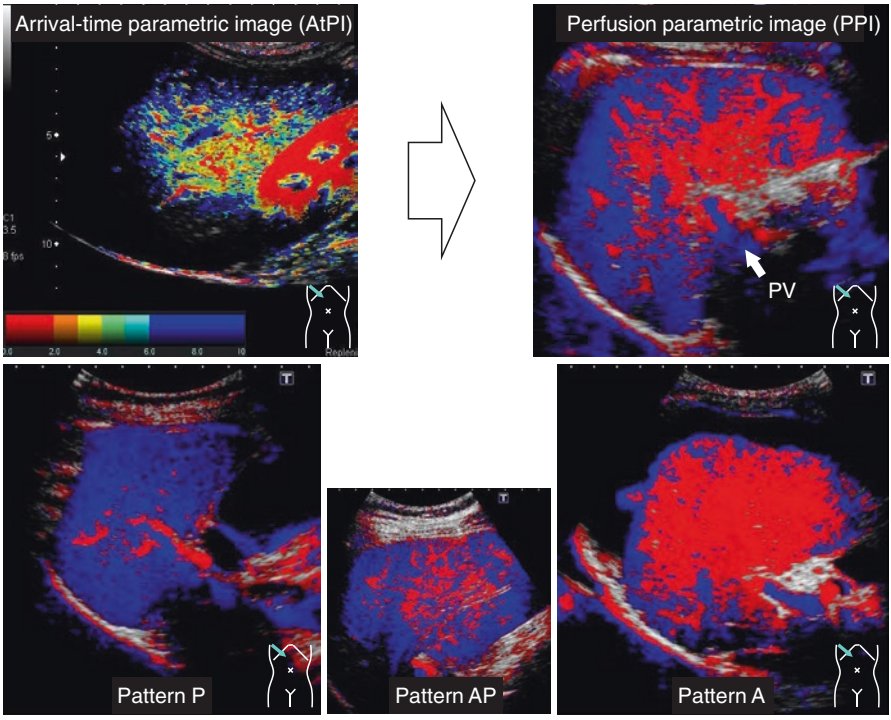


Fig. 10.3 Perfusion parametric image: The arrival-time parametric image is further divided into two using the arrival time in portal vein. Pixels that opacify faster than the arrival time of the portal vein are colored red, while pixels that arrive slower are colored blue. Red represents the pixels supplied with Sonazoid® bubbles by the arteries. If the entire image is red, we refer to this as A (artery) pattern A (the artery pattern), and if the entire image is blue, we refer to this as pattern P (the portal pattern), and anything in between is referred to as pattern AP

pattern A, and if the entire image is blue, we refer to this as pattern P, and anything in between is referred to as pattern AP. This is readily understandable (Fig. 10.3).

10.2.4 Arterialization Ratio (AR)

By classifying patterns using PPI, we can understand what is happening in the patient, but in order to perform a comparative investigation with other clinical findings and other test data, it is necessary to convert the degree of arterialization into numeric form. Hence, the authors have employed image analysis software (pixel count, Toshiba Medical Systems Corporation) and used the images depicted to calculate the ratio (percentage) of red opacified pixels in relation to the total number of opacified pixels throughout the entire liver and defined this as the arterialization ratio (AR).

Here, we show the results including some practical examples as this method made it possible to investigate various hepatic diseases.

10.3 Chronic Viral Liver Disease

10.3.1 Diagnosis of Lesion Progression (Staging)

When chronic hepatitis has been diagnosed, the next important step is staging. Staging is used to select treatment methods and determine the degree of urgency. The stage is represented by the degree of fibrosis: healthy liver is F0, liver cirrhosis is F4, and chronic hepatitis is distributed between F1 and F3 [14].

10.3.1.1 Investigation Using AtPI

As mentioned previously, the healthy liver exhibits pattern P, and the parenchyma opacifies slowly, while liver cirrhosis exhibits pattern A and opacifies rapidly. Intermediate lesions between the two extremes, i.e., stage F1–F3 chronic hepatitis, should present with a speed of findings between A and P. Consequently, we studied the speed and delay of arrival using AtPI in 141 patients with histologically proven chronic liver disease due to hepatitis C virus (HCV) [15]. First, we identified from a pilot study in a small number of subjects that the time required for opacification of the entire liver was approximately 10 s; therefore we used an interval of 5 s as the cutoff point to divide the AtPI into two colors. Images before this were red, and any images thereafter were yellow; that is, red was fast and yellow was slow. The AtPI images obtained were classified by stage, and we found that in stage F1, they were obviously yellow, while red increased as fibrosis progressed to F2, F3, and F4 (Fig. 10.4). For this reason, we used additional image analysis software (Image J) and determined the ratio (percentage) of red in relation to the total number of opacified pixels. A comparison by F stage is shown in the Fig. 10.5. As the F stages progress, the ratio of red increases significantly, and it is clear that the AtPI is useful as a tool for understanding lesion progression.

10.3.1.2 Investigation Using PPI

Assuming that the outcome of AtPI reflects the arterialization of the hepatic sinusoidal blood flow in association with lesion progression, it is highly likely that more favorable outcomes will be obtained using PPI, which is able to clearly determine the arterialization. Therefore, we performed similar investigations using the AR obtained during PPI (Fig. 10.6) and noted although the AR tended to increase gradually from F0 to F3, no significant differences were observed. Significant differences only occurred when liver cirrhosis progressed to stage F4. While AtPI accurately reflects the progression of lesions from F0 to F4, the same cannot be said of the AR determined using PPI. These results were anticipated, although they were different from our initial assumptions. Investigations performed by various institutions to date have stated that the mechanism of arterialization during chronic liver disease is

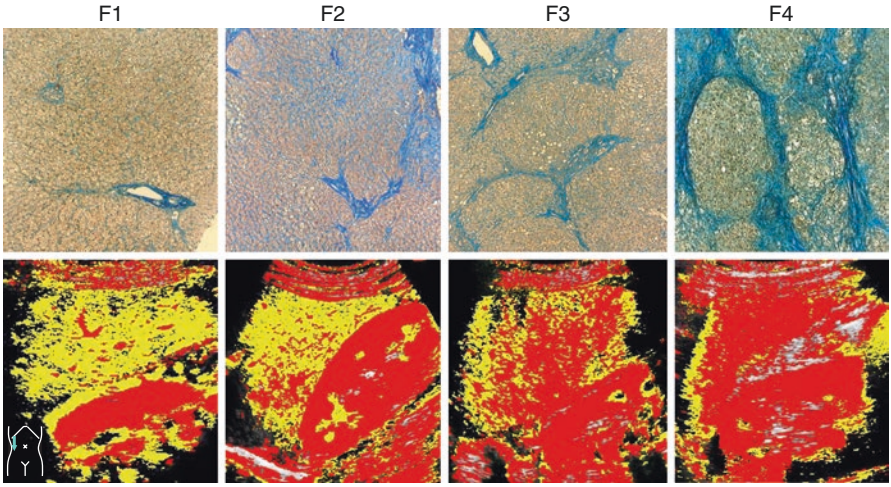


Fig. 10.4 The arrival-time parametric image is divided into two colors using an interval of 5 s from $t = 0$ as the cutoff point. Pixels before this were red, and any pixels thereafter were yellow; that is, red was fast and yellow was slow. This arrival-time parametric image showed that red increased as they progress through stages F2, F3, and F4 (quoted from Wakui N: J Ultrasound Med 2012; 31: 373–82)

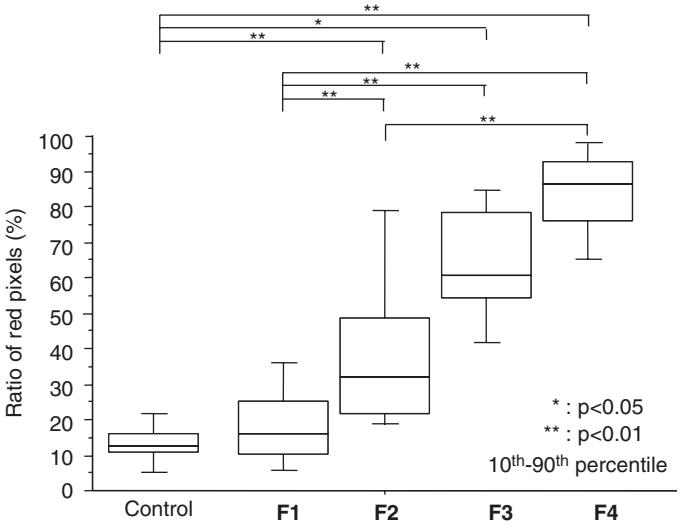


Fig. 10.5 Image analysis software (Image J) was employed and determined the ratio of red in relation to the total number of opacified pixels. As the F stages progress, the ratio of red increases significantly (quoted from Wakui N: J Ultrasound Med 2012; 31: 373–82)

reduced portal vein blood flow in the hepatic parenchyma. The hypothesis states that intrahepatic adenosine concentration increases when the portal vein blood flow decreases, causing dilation of the hepatic artery and resulting in arterialization [9]. This is said to be a compensatory mechanism of the hepatic artery during portal hypertension. Therefore, in advanced chronic liver disease, hepatic arterial

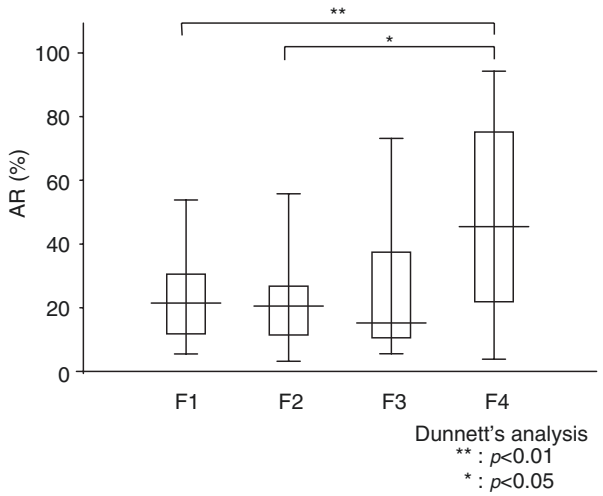


Fig. 10.6 Arterialization ratio (AR) obtained during perfusion parametric image was classified by fibrosis stage. Although the AR tended to increase gradually as fibrosis progresses from F0 to F3, no significant difference was observed. Significant differences only occurred in hepatic cirrhosis

dominance is induced, and AR is increased only when the conditions are bad enough to cause portal hypertension. Meanwhile, the outcomes obtained using AtPI show an increase in the speed of the hepatic parenchymal blood flow, which is not synonymous with arterialization. It includes other factors affecting the increase in intrahepatic blood flow speed in addition to arterialization, such as the onset of vascular shunts within the hepatic parenchyma associated with inflammation, necrosis or scarring, and entering a systemic circulatory hyperdynamic state. Therefore, AtPI starts to change before becoming liver cirrhosis, and when liver cirrhosis is accompanied by all these factors, the acceleration of hepatic blood flow is enhanced, and as a result, it shows a good correlation to progression through the various disease stages. Accordingly, we believe that AtPI is a useful tool for understanding the degree of lesion advancement in chronic liver disease, while PPI is a useful tool for understanding arterialization and gaining insight into the disease state.

Through this investigation, we have elucidated that in conjunction with the progression of lesions, parenchymal perfusion gradually changes from being of portal vein origin to hepatic artery origin. Furthermore, we show that this phenomenon can be visualized by anyone who performs Sonazoid® CEUS in a clinical setting.

10.3.2 Portal Hypertension

The progression of hepatic lesions and fibrosis causes the progression of portal hypertension, and the arterialization of parenchymal perfusion increases the sinusoidal pressure, which may thereby further exacerbate portal hypertension. Thus,

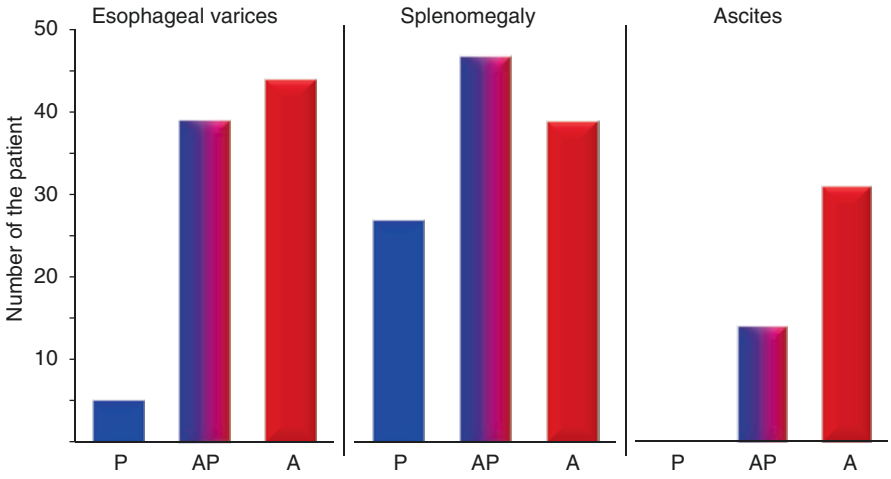


Fig. 10.7 Relationship of the pattern of the perfusion parametric image (A, AP, P) with esophageal varices, splenomegaly, and ascites in 154 patients with F3/4 liver disease

we investigated the relationship of arterialization with esophageal varices, splenomegaly, and ascites in 154 cases of F3/4 liver disease with a high likelihood of causing portal hypertension using PPI [16]. Results show that with the exception of splenomegaly, pattern A occurred more frequently in patients with esophageal varices and ascites (Fig. 10.7). Splenomegaly does not necessarily correlate to portal vein pressure, which we consider consistent. A complete understanding of arterialization gained by using PPI is also highly likely to be useful for diagnosing portal hypertension.

10.4 Portal Vein Thrombosis

Portal vein thrombosis is not a liver disease, but because of the possibility that decreased portal venous blood flow causes arterialization of the hepatic parenchymal perfusion, we investigated two patients with portal vein thrombosis so as to examine its reversibility. Both patients developed bacterial infection of the portal vein due to colonic diverticulitis, and acute portal vein thrombosis occurred in them. No blood flow was detected in the right branch of the portal vein during the acute phase, and the region of perfusion was completely arterialized. However, in regions where portal vein blood flow was reestablished by means of thrombolysis, PPI performed during recanalization showed that blood flow had returned to a pattern P. In other words, a reduction in portal vein blood flow causes compensatory arterialization, and we have determined that these changes are reversible.

10.5 Idiopathic Portal Hypertension (IPH)

This is portal hypertension of unknown etiology and is suspected if splenomegaly or extrahepatic collateral pathways (varices rupture in particular) are observed, despite there being no findings suggestive of hepatitis or hepatic cirrhosis in the liver itself. The diagnosis is supported if the hepatic veins form a "weeping willow" pattern and if other findings indicate the presence of shunts between the hepatic veins. Histologically, occlusion and disappearance of the peripheral branches of the portal vein and the appearance of abnormal collateral vessels surrounding Glisson's capsule are pathognomonic [17, 18]. Although some of these findings contribute to diagnosis, they are all insufficient for making a definitive diagnosis. Consequently, we investigated parenchymal perfusion findings in three of our own cases, focusing on the histological occlusion in the peripheral portal veins. Results showed that all cases exhibited pattern A during PPI. Similar to portal vein thrombosis, occlusion and obliteration of the peripheral branches of the portal vein reduces the amount of blood flow entering the sinusoids, which may cause compensatory arterialization. The investigation included a small population of three cases and does not provide much information. However, if arterialization of the hepatic parenchymal perfusion is observed in cases with portal hypertension that have no underlying liver disease or portal vein thrombosis and no history of alcohol consumption, then the likelihood of this disease is high.

10.6 Conclusions

In this article, we have reviewed the diagnostic significance and utility of first pass Sonazoid® CEUS, by presenting several diseases that cause portal hypertension, including liver cirrhosis. Much information can be obtained during the late vascular phase and the Kupffer phase of cirrhosis, but currently we are gathering and analyzing data and will discuss the findings in due course.

CEUS is a functional imaging modality and does not advance the diagnosis of liver disease on a morphological basis. However, it can play a considerable role in understanding the respective complicated disease states that occur in liver disease, and we have already started to use it during clinical practice.

References

1. Reuter SR, Redman HC. Gastrointestinal angiography. Philadelphia: WB Sounders; 1977. p. 306–55.
2. Lautt WW, Legare DJ, D'Almeida MS. Adenosine as putative regulator of hepatic arterial flow (the buffer response). Am J Physiol. 1985;248:H331–8.

3. Oda M, Kan S, Yokomori H. Regulatory mechanisms of the hepatic microcirculation. In: Miura Y, Itai Y, editors. Macroscopical observation of the hepatic microcirculation and of the characteristic blood flow of the liver tumor. Tokyo: Medical Tribune; 2000. (Japanese).
4. Miura Y. Regulatory mechanisms of the portal blood flow observed from the point of point of TAE. In: Miura Y, Itai Y, editors. Macroscopical observation of the hepatic microcirculation and of the characteristic blood flow of the liver tumor. Tokyo: Medical Tribune; 2000. (Japanese).
5. Zhang Q, Yuan ZG, Wang DQ, et al. Perfusion CT findings in liver of patients with tumor during chemotherapy. World J Gastroenterol. 2010;16:3202–5.
6. Takahashi H, Suzuki M, Ikeda H, et al. Evaluation of quantitative portal venous, hepatic arterial, and total hepatic tissue blood flow using Xenon CT in alcoholic liver cirrhosis comparison with liver cirrhosis C. Alcohol Clin Exp Res. 2007;31:43–8S.
7. Hashimoto K, Murakami T, Dono K, et al. Assessment of the severity of liver disease and fibrotic change: the usefulness of hepatic CT perfusion imaging. Oncol Rep. 2006;16:677–83.
8. Moreno AH, Rousselot LM, Panke WF, et al. The rate of hepatic blood flow in normal subjects and in patients with portal hypertension. Surg Gynecol Obstet. 1960;111:443–50.
9. Sarpar R, Fajman WA, Rypins EB, et al. A noninvasive method for measuring portal venous-total hepatic blood flow by hepato-splenic radio-nuclide angiography. Radiology. 1989;141:179–84.
10. Shimada K. Clinical evaluation of the hepatic hemodynamics using 99mTc-DTPA-HAS scintiangiography in patients with viral chronic liver disease. Kanzo. 1994;35:11–8. (Japanese).
11. Sumino Y, Wakui N, Takayama R, et al. Ultrasonographic diagnosis of the liver diseases. Jpn J Med Ultasonics, 2009. 36:301–18. (Japanese).
12. Sumino Y, Takayama R, Nakajima S, et al. Ultrasound of the diffuse liver diseases. Kan-Tan-Sui. 2010;60:395–407. (Japanese).
13. Sumino Y, Wakui N, Takayama R. Usefulness of the blood flow analysis with using the contrast enhanced ultrasound in patient with liver disease. INNERVISION. 2011;26:36–8. (Japanese).
14. Ichida F, Omata M, Tsuji T, et al. Histopathological diagnostic criterion of the chronic hepatitis. In: Inuyama symposium, Chugai Co., Tokyo; 1996, p. 183–8. (Japanese).
15. Wakui N, Takayama R, Kanekawa T, et al. Usefulness of arrival time parametric imaging in evaluating the degree of liver disease progression in chronic hepatitis C infection. J Ultrasound Med. 2012;31:373–82.
16. Wakui N, Takayama R, Kanekawa T, et al. Usefulness of parametric imaging in analyzing the portal blood flow. Jpn J Portal Hypertens. 2012;18:14–8. (Japanese).
17. Nakanuma Y, Kouda A, Katayanagi K. Pathology of the idiopathic portal hypertension. Kan-Tan-Sui. 1999;38:35–41. (Japanese).
18. Sato Y, Kitamura S, Kitao A, et al. Pathology and pathogenesis of idiopathic portal hypertension. Kan-Tan-Sui. 2010;61:133–40. (Japanese).

Chapter 11
Liver and Spleen Stiffness Measurement

Yoshihiro Furuichi and Fuminori Moriyasu

Abstract Esophageal varices (EV) are often complicated in cirrhotic patients, and bleeding from EV induces high mortality rate. Endoscopic screening for EV and hepatic venous pressure gradient (HVPG) is recommended for all cirrhotic patients; however, these are invasive procedures. Liver stiffness (LS) measurement (LSM) is a noninvasive technique using elastographic method by ultrasonography or magnetic resonance imaging and is a very useful examination method to assess significant fibrosis and to rule out liver cirrhosis (LC). LS values are thought to increase gradually alongside the increment of HVPG in line with the progresses of LC state. However, regarding the presence of EV, spleen stiffness (SS) is a more accurate predictor with high area under receiver operating characteristic curve than LS. The measurement of SS values can reveal cirrhotic patients with high-risk EV. Moreover, measuring the spleen/liver stiffness ratio by elastography made it possible to noninvasively, specifically, and accurately diagnose idiopathic portal hypertension or extrahepatic portal vein obstruction.

Keywords Liver stiffness · Spleen stiffness · Esophageal varices · Portal hypertension · Ultrasonography · Elastography · Idiopathic portal hypertension · Extrahepatic portal vein obstruction

11.1 Introduction

Esophageal varices (EV) are often complicated in cirrhotic patients, and bleeding from EV is associated with a high mortality rate. Endoscopic screening for EV is recommended for all cirrhotic patients, and frequent surveillance depending on the

Y. Furuichi (✉)
Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, Japan
e-mail: furuich@tokyo-med.ac.jp

F. Moriyasu
Department of Gastroenterology and Hepatology, Sanno Hospital, Tokyo, Japan
e-mail: moriyasu@iuhw.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_11

size and treatment of varices is recommended. Recent studies have shown that spleen stiffness (SS) correlates with hepatic fibrosis and portal hypertension in patients with chronic liver disease. Subsequent published studies have suggested that SS measurement (SSM) can predict the presence and size of EV in patients with chronic liver disease with high diagnostic accuracy.

11.2 The Clinical Importance of Hepatic Vein Portal Gradient

When the hepatic venous pressure gradient (HVPG) is more than 5 mmHg, it is diagnosed as portal hypertension. HVPG is measured by calculating the difference between wedged and free pressures in the hepatic vein. Clinically significant portal hypertension (CSPH) is diagnosed when HVPG is more than 10 mmHg, and the risk of developing ascites or EV is much higher at this value. If HVPG is more than 12 mmHg, the risk of variceal bleeding increases and development of ascites occurs [1]. The calculation of HVPG is considered as a better indicator of liver function [2]. Based on these findings, measurement of HVPG is recommended for all cirrhotic patients at the time of diagnosis for risk and prognosis assessment [3, 4]. But, despite its excellent diagnostic and prognostic value, HVPG is an invasive procedure available only in specialized centers, and therefore it has not been performed in many hospitals [5].

11.3 Elastography

Elastographic method was developed and enabled us to measure liver and spleen stiffness in recent years. Elastographic methods are divided into two major categories, magnetic resonance elastography and ultrasonographic elastography. Furthermore, ultrasonographic methods are divided into two categories, strain elastography and shear wave elastography. The former method (e.g., real-time tissue elastography) is calculated by the strain, which is induced by the passive power of the compression or the cardiac beat. The latter method (e.g., transient elastography or virtual touch tissue quantification (VTTQ) (ARFI) elastography) uses a shear wave. Transient elastography is performed using a vibrator probe which transmits low-frequency vibrations to the tissue, inducing an elastic shear wave, and the stiffness is shown as Young's modulus. On the other hand, in VTTQ (ARFI) elastography, these shear waves are induced by an acoustic push pulse from the probe, and the speed of shear wave is calculated by a detection pulse. As a result we can estimate the stiffness of the tissue as the spread speed of the shear wave. The weak point

in real-time tissue elastography is that the elasticity cannot be expressed as an absolute value, and the elastic ratio among two regions of interest can only be calculated. In other words, the acquired value (=ratio) lacks objectivity. Meanwhile, the weak point in transient elastography is that the system does not have a B-mode, and this measurement should be performed in the A-mode or M-mode, which demands higher examiner skill.

11.4 Liver Stiffness Measurement

Liver stiffness (LS) measurement (LSM) is a noninvasive technique using the elastographic method by ultrasonography or magnetic resonance imaging (MRI) [6]. It is a very useful examination method to assess significant fibrosis and to rule out cirrhosis in patients with liver disease [7]. LSM by transient elastography exhibits excellent accuracy for diagnosis of cirrhosis. When the cutoff value was set as 13.2 kPa, the area under the receiver operating characteristic curve (AUROC) was 0.970 in the single center study, and moreover the best cutoff value appeared to be 13.01 kPa in this meta-analysis study [8]. There is a report about the complications and cutoff value of LSM. It showed 27.5 kPa for large EV; 37.5 kPa for Child B or C cirrhosis; 49.1 kPa for development of ascites; 53.7 kPa for development of hepatocellular carcinoma; and 62.7 kPa for variceal bleeding [9]. A strong positive correlation was found between LS and HVPG in patients with HCV-related liver disease and advanced fibrosis (Inuyama classification; F3–F4) ($r2 = 0.61$, $P < 0.0001$) [10, 11]. LS values were thought to increase gradually alongside the increment of HVPG in line with the progresses of the LC state [12].

LS can also assess the clinical course of chronic liver disease patients. There is a report demonstrating a five times higher risk developing hepatocellular carcinoma in HCV patients for which the baseline value of LS was higher than 25.0 kPa compared with those with values lower than 10.5 kPa [13]. In another retrospective study, LS was able to predict the 5-year overall survival rate [10]. When the baseline value of LS was under 9.5 kPa, the rate was 96%, and a value of over 40.0 kPa indicated a 47% 5-year survival rate. Moreover, when the baseline value of LS was more than 14.0 kPa, it predicted a worse prognosis about the appearance of complications. These findings are fully supported by a recent meta-analysis [14].

CSPH can be diagnosed by LS with a 90% sensitivity and a 80% specificity [15]. For the presence of EV, LS showed lower AUROC values, between 0.76 and 0.84. For cutoff values of 13.9, 17.6, and 21.1 kPa, respectively, LS showed a good sensitivity (0.95, 0.9, and 0.79) but a lower specificity (0.43, 0.43, and 0.7) [16]. There are a lot of studies calculating the cutoff values of LS for diagnosing CSPH (Table 11.1). However, regarding the presence of EV, spleen stiffness (SS) can be predicted more accurately with high AUROC than with LS.

Table 11.1 Relation between liver stiffness and portal hypertension

Author	Year	Number of patients	Best cutoff value of LS for CSPH (kPa)	Correlation coefficient between LS value and HVPG (*r*)	AUROC
Kazemi et al. [16]	2006	165	13.9 (for detection of EV)	–	0.84 (95% CI 0.78–0.90)
Vizzutti et al. [11]	2007	61	13.6	0.61	0.99 (95% CI 0.92–0.99)
Lemoine et al. [17]	2008	92	20.5 for HCV 34.9 for ALC	0.53	0.84 (95% CI 0.80–0.88)
Bureau et al. [18]	2008	150	21.0	0.858	0.945 (95% CI 0.904–0.987)
Reiberger et al. [19]	2012	502	18.0	0.794	0.817 (95% CI 0.752–0.891)
Llop et al. [20]	2012	79	21.0	0.552	0.840 (95% CI 0.748–0.933)
Berzigotti et al. [21]	2013	117	20.6	–	0.883 (95% CI 0.824–0.943)
Hong et al. [22]	2013	59	21.95	0.496	0.851 (95% CI 0.752–0.949)
Salzl et al. [23]	2014	88	16.8	0.765	0.870
Zykus et al. [24]	2015	107	17.4	0.75	0.949
Procopet et al [25]	2015	202	21.1	–	0.94 (95% CI 0.89–0.99)
Kitson et al [26]	2015	95	29.0	0.38	0.90 (95% CI 0.83–0.97)
Elkrief et al. [27]	2015	79	24.5 (SWE)	0.289	0.87 (95% CI 0.78–0.95)
Schwabl et al. [28]	2015	226	16.1	0.836	0.957

LS liver stiffness, *CSPH* clinically significant portal hypertension, *HVPG* hepatic venous pressure gradient, *AUROC* area under receiver operating characteristic curve, *EV* esophageal varices, *HCV* hepatic C virus, *ALC* alcoholic, *SWE* shear wave elastography, *CI* confidence interval

11.5 Spleen Stiffness Measurement

Splenomegaly is one of the most important clinical signs used for diagnosis of portal hypertension. Splanchnic congestion and fibrosis were discussed as generating factors for splenomegaly [29]. Recently SSM using elastography was found to assess the portal hypertension state more accurately than LSM. Initial data about SSM came from MRI studies, conducted on 35 patients with varying degrees of chronic liver disease and 12 healthy volunteers, using an elastography protocol, which found a highly significant correlation between liver and SS in patients with portal hypertension [30]. SSM using the ultrasound method (real-time tissue elastography) was subsequently reported, which indicated that splenic elasticity and HVPG showed significant linear correlation ($R = 0.85$, $P < 0.0001$) and that the diagnostic accuracy of cutoff values of 8.24 for splenic elasticity in predicting the

presence of gastroesophageal varices was 90% (sensitivity 96%; specificity 85%; positive predictive value (PPV) 83%; negative predictive value (NPV) 97%) [31]. Another group reported that as SS cutoff value of 46.4 kPa using transient elastography showed a good accuracy (AUROC = 0.781) and a high PPV (93.4%) in predicting esophageal varices [32]. SS exhibits better sensitivity (for the same specificity) than LS to rule in the presence of the EV and portal hypertension stages (both HVPG > 10 and HVPG > 12) [33]. The other study showed that SS values can reveal cirrhotic patients with high-risk EVs. A SS cutoff value of 3.18 m/s identified patients with low-risk EVs, and the value of 3.30 m/s identified patients with high-risk EVs with 98.9% sensitivity and 72.1% accuracy [34]. The data from each institution is shown in Table 11.2. These elevated SS values were considered to be caused by congestion of the red pulp, tissue hyperplasia, and diffuse fibrosis of spleen trabeculae [40].

11.6 Diagnostic Method of Aberrant Portal Hemodynamics by Elastography

Idiopathic portal hypertension (IPH) is a disease in which occlusion and narrowing of peripheral portal veins in the liver leads to portal hypertension and is frequently misdiagnosed as LC, because some IPH cases are very difficult to distinguish from cirrhosis on radiological examinations. Our study revealed that measuring the spleen/liver stiffness ratio with elastography made it possible to noninvasively, specifically, and accurately diagnose IPH (the AUROC was 0.933, sensitivity 0.941, specificity 0.800, and accuracy 0.839), because the stiffness of the liver in IPH was relatively soft and that of the spleen was the hardest among the liver disease groups [40]. This increased SS was thought to be a manifestation of splenic fibrosis and congestion. The degree of LS in the IPH group was about the same level as that in the chronic hepatitis group with early stage of fibrosis, suggesting that mild fibrosis occurred only in the parts of the liver limited to the periphery of the portal vein.

In another study, LS and SS were measured in 65 consecutive patients with extrahepatic portal vein obstruction (EHO). The LS ($P = 0.001$) and SS ($P = 0.01$) values were higher in patients with EHO (6.7 kPa ± 2.3 and 51.7 kPa ± 21.5, respectively) than in control subjects (4.6 kPa ± 0.7 and 16.0 kPa ± 3.0, respectively). Patients who exhibited bleeding had higher SS than those who did not (60.4 kPa ± 5.4 vs. 30.3 kPa ± 14.2, $P = 0.01$) [41].

11.7 Conclusion

LS became an independent variable associated with the presence of portal hypertension-related complications, risk of decompensation, and risk of fatality. Similarly, SS appears to be a better means of assessing portal hypertensive

Table 11.2 Relation between spleen stiffness and esophageal varices prediction

Author	Year	Number of patients	Technique	Best cutoff value of SS for EV prediction	Correlation coefficient between SS value and HVPG (*r*)	AUROC
Hirooka et al. pilot [31]	2011	60	RTE	8.24 (ratio to small vein)	0.854	0.978 (95% CI 0.902–0.999)
Hirooka et al. validation [31]	2011	190	RTE	8.24 (ratio to small vein)	–	–
Stefanescu et al. [32]	2011	137	TE	46.4 kPa	–	0.781 (Accuracy 80.45%)
Bota et al. [35]	2012	145	ARFI	2.55 m/s	–	0.578 (Accuracy 53.1 %)
Colecchia et al. [33]	2012	113	TE	55.0 kPa	0.78	0.941 (95% CI 0.90–0.98)
Vermehren et al. [36]	2012	166	ARFI TE	4.13 m/s 48.5 kPa	–	0.58 (95% CI 0.49–0.67) 0.53 (95% CI 0.44–0.63)
Ye et al. [37]	2012	73	ARFI	3.16 m/s	–	0.83 (Se 84.1%, Sp 81.0%)
Takuma et al. [34]	2013	340	ARFI	3.18 m/s	–	0.933 (95% CI 0.906–0.960)
Elkrief et al. [27]	2015	33 77	TE SWE	56.3 kPa (for CSPH) 34.7 kPa (for CSPH)	– –	(Accuracy 73%) (Accuracy 47%)
Kim et al. [38]	2015	125	ARFI	3.16 m/s 3.40 m/s (for hemorrhage)	–	0.785 (95% CI 0.703–0.866) 0.813 (95% CI 0.738–0.889)
Takuma et al. [39]	2016	60	ARFI	3.36 m/s	0.876	0.943 (95% CI 0.852–0.987)

SS spleen stiffness, *EV* esophageal varices, *HVPG* hepatic venous pressure gradient, *AUROC* area under receiver operating characteristic curve, *RTE* real-time tissue elastography, *TE* transient elastography, *ARFI* acoustic radiation force impulse, *SWE* shear wave elastography, *CI* confidence interval

complications and predicting the occurrence of EV in cirrhotic patients, and there is growing evidence that it also plays an important role in prognosis. We think elastographic examination has infinite possibilities, because it allows physicians to noninvasively diagnose not only LC but also aberrant portal hemodynamics.

References

1. Bosch J, Garcia-Pagán JC, Berzigotti A, Abraldes JG. Measurement of portal pressure and its role in the management of chronic liver disease. Semin Liver Dis. 2006;26:348–62.
2. Burroughs AK, Groszmann R, Bosch J, Grace N, Garcia-Tsao G, Patch D, et al. Assessment of therapeutic benefit of antiviral therapy in chronic hepatitis C: is hepatic venous pressure gradient a better end point? Gut. 2002;50:425–7.
3. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46:922–38.
4. de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2010;53:762–8.
5. Targownik LE, Spiegel BM, Dulai GS, Karsan HA, Gralnek IM. The cost-effectiveness of hepatic venous pressure gradient monitoring in the prevention of recurrent variceal hemorrhage. Am J Gastroenterol. 2004;99:1306–15.
6. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, Christidis C, Ziol M, Poulet B, Kazemi F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol. 2003;29:1705–13.
7. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology. 2008;134:960–74.
8. Lupsor Platon M, Stefanescu H, Feier D, Maniu A, Badea R. Performance of unidimensional transient elastography in staging chronic hepatitis C. Results from a cohort of 1,202 biopsied patients from one single center. J Gastrointestin Liver Dis. 2013;22:157–66.
9. Vergniol J, Foucher J, Terrebonne E, Bernard PH, le Bail B, Merrouche W, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology. 2011;140:1970–79, 1979.e1–3.
10. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, Petrarca A, Moscarella S, Belli G, Zignego AL, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology. 2007;45:1290–7.
11. Ichida F, Tsuji T, Omata M, Ichida T, Inoue K, et al. New Inuyama Classification for histological assessment of chronic hepatitis. Hepatol Commun. 1996;6:112–9.
12. Reiberger T, Ferlitsch A, Payer BA, Pinter M, Homoncik M, Peck-Radosavljevic M. Non-selective β-blockers improve the correlation of liver stiffness and portal pressure in advanced cirrhosis. J Gastroenterol. 2012;47:561–8.
13. Masuzaki R, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T, et al. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology. 2009;49:1954–61.
14. Robic MA, Procopet B, Métivier S, Péron JM, Selves J, Vinel JP, et al. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. J Hepatol. 2011;55:1017–24.
15. Shi KQ, Fan YC, Pan ZZ, Lin XF, Liu WY, Chen YP, et al. Transient elastography: a meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. Liver Int. 2013;33:62–71.

16. Kazemi F, Kettaneh A, N'kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, Beaugrand M. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol. 2006;45:230–5.
17. Lemoine M, Katsahian S, Ziol M, Nahon P, Ganne-Carrie N, Kazemi F, et al. Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis. Aliment Pharmacol Ther. 2008;28:1102–10.
18. Bureau C, Metivier S, Peron JM, Selves J, Robic MA, Gourraud PA, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. Aliment Pharmacol Ther. 2008;27:1261–8.
19. Reiberger T, Ferlitsch A, Payer BA, Pinter M, Schwabl P, Stift J, et al. Noninvasive screening for liver fibrosis and portal hypertension by transient elastography–a large single center experience. Wien Klin Wochenschr. 2012;124:395–402.
20. Llop E, Berzigotti A, Reig M, Erice E, Reverter E, Seijo S, et al. Assessment of portal hypertension by transient elastography in patients with compensated cirrhosis and potentially resectable liver tumors. J Hepatol. 2012;56:103–8.
21. Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, García-Pagán JC, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology. 2013;144:102–111.e1.
22. Hong WK, Kim MY, Baik SK, Shin SY, Kim JM, Kang YS, et al. The usefulness of noninvasive liver stiffness measurements in predicting clinically significant portal hypertension in cirrhotic patients: Korean data. Clin Mol Hepatol. 2013;19:370–5.
23. Salzl P, Reiberger T, Ferlitsch M, Payer BA, Schwengerer B, Trauner M, et al. Evaluation of portal hypertension and varices by acoustic radiation force impulse imaging of the liver compared to transient elastography and AST to platelet ratio index. Ultraschall Med. 2014;35:528–33.
24. Zykus R, Jonaitis L, Petrenkienė V, Pranculis A, Kupčinskas L. Liver and spleen transient elastography predicts portal hypertension in patients with chronic liver disease: a prospective cohort study. BMC Gastroenterol. 2015;15:183.
25. Procopet B, Cristea VM, Robic MA, Grigorescu M, Agachi PS, Metivier S, et al. Serum tests, liver stiffness and artificial neural networks for diagnosing cirrhosis and portal hypertension. Dig Liver Dis. 2015;47:411–6.
26. Kitson MT, Roberts SK, Colman JC, Paul E, Button P, Kemp W. Liver stiffness and the prediction of clinically significant portal hypertension and portal hypertensive complications. Scand J Gastroenterol. 2015;50:462–9.
27. Elkrief L, Rautou PE, Ronot M, Lambert S, Dioguardi Burgio M, Francoz C, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology. 2015;275:589–98.
28. Schwabl P, Bota S, Salzl P, Mandorfer M, Payer BA, Ferlitsch A, et al. New reliability criteria for transient elastography increase the number of accurate measurements for screening of cirrhosis and portal hypertension. Liver Int. 2015;35:381–90.
29. Bolognesi M, Merkel C, Sacerdoti D, Nava V, Gatta A. Role of spleen enlargement in cirrhosis with portal hypertension. Dig Liver Dis. 2002;34:144–50.
30. Talwalkar JA, Yin M, Venkatesh S, Rossman PJ, Grimm RC, Manduca A, et al. Feasibility of in vivo MR elastographic splenic stiffness measurements in the assessment of portal hypertension. AJR Am J Roentgenol. 2009;193:122–7.
31. Hirooka M, Ochi H, Koizumi Y, Kisaka Y, Abe M, Ikeda Y, et al. Splenic elasticity measured with real-time tissue elastography is a marker of portal hypertension. Radiology. 2011;261:960–8.
32. Stefanescu H, Grigorescu M, Lupsor M, Procopet B, Maniu A, Badea R. Spleen stiffness measurement using Fibroscan for the noninvasive assessment of esophageal varices in liver cirrhosis patients. J Gastroenterol Hepatol. 2011;26:164–70.
33. Colecchia A, Montrone L, Scaioli E, Bacchi-Reggiani ML, Colli A, Casazza G, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology. 2012;143:646–54.

34. Takuma Y, Nouso K, Morimoto Y, et al. Measurement of spleen stiffness by acoustic radiation force impulse imaging identifies cirrhotic patients with esophageal varices. Gastroenterology. 2013;144:92–101.e2.
35. Bota S, Sporea I, Sirli R, Focsa M, Popescu A, Danila M, et al. Can ARFI elastography predict the presence of significant esophageal varices in newly diagnosed cirrhotic patients? Ann Hepatol. 2012;11:519–25.
36. Vermehren J, Polta A, Zimmermann O, Herrmann E, Poynard T, Hofmann WP, et al. Comparison of acoustic radiation force impulse imaging with transient elastography for the detection of complications in patients with cirrhosis. Liver Int. 2012;32:852–8.
37. Ye XP, Ran HT, Cheng J, Zhu YF, Zhang DZ, Zhang P, et al. Liver and spleen stiffness measured by acoustic radiation force impulse elastography for noninvasive assessment of liver fibrosis and esophageal varices in patients with chronic hepatitis B. J Ultrasound Med. 2012;31:1245–53.
38. Kim HY, Jin EH, Kim W, Lee JY, Woo H, Oh S, et al. The role of spleen stiffness in determining the severity and bleeding risk of esophageal varices in cirrhotic patients. Medicine (Baltimore). 2015;94:e1031.
39. Takuma Y, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Takabatake H, et al. Portal hypertension in patients with liver cirrhosis: diagnostic accuracy of spleen stiffness. Radiology. 2016;279:609–19.
40. Furuichi Y, Moriyasu F, Taira J, Sugimoto K, Sano T, Ichimura S, et al. Noninvasive diagnostic method for idiopathic portal hypertension based on measurements of liver and spleen stiffness by ARFI elastography. J Gastroenterol. 2013;48:1061–8.
41. Sharma P, Mishra SR, Kumar M, Sharma BC, Sarin SK. Liver and spleen stiffness in patients with extrahepatic portal vein obstruction. Radiology. 2012;263:893–9.

Chapter 12
Portal Vein Hemodynamics: 3DCT

Naoya Murashima and Satoshi Nakayama

Abstract In patients with portal hypertension, portosystemic venous collateral pathways are frequently formed. Three-dimensional computed tomography (3DCT) using multidetector computed tomography (MDCT) is one of the most important modalities for detecting collaterals because of its high resolution and whole body scanning features. The method of constructing 3DCT images and representative collateral pathways are described in this chapter.

Keywords 3DCT · MDCT · Portosystemic shunt · Collaterals

12.1 Significance of Portal Vein Collaterals in Portal Hypertension

12.1.1 Portal Hypertension and Portosystemic Collaterals

Portosystemic venous collateral pathways are frequently formed as a result of portal hypertension. The presence of these portal collaterals is usually evidence of portal hypertension. A famous physical finding is distended varicose veins of the abdominal wall, known as a caput medusae. Esophageal varices may be interpreted as collaterals in the hemiazygos venous system. In addition, numerous microcollaterals in the liver that do not supply the liver lobules in the setting of liver cirrhosis or idiopathic portal hypertension can also be considered to be part of the portosystemic collateral circulation.

N. Murashima (✉) · S. Nakayama
Department of Gastroenterology, Mishuku Hospital, Tokyo, Japan
e-mail: murashima@mishuku.gr.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_12

12.1.2 Portal Vein Collaterals: A Historical Background

Surgeons in the 1950s [1] identified apparent collaterals (Fig. 12.1) during selective shunt surgery. Prof. Lunderquist in Sweden first performed percutaneous transhepatic portography (PTP) [2] in the early 1960s without laparotomy. PTP involved forcibly injecting contrast medium through a catheter inserted through the portal vein, allowing for detection of all small vessels in the abdominal cavity. The locations of collaterals identified by PTP are shown in Table 12.1. However, PTP is invasive in nature, so it has not been widely used in Japan. The 1990s saw the introduction of multidetector computed tomography (MDCT), which is minimally invasive and involves short examination times. During one breath hold, MDCT can scan not only the thorax but also the abdomen. Further, advanced computer processing methods make 3D analysis possible, and many software programs to perform the analysis have become available.

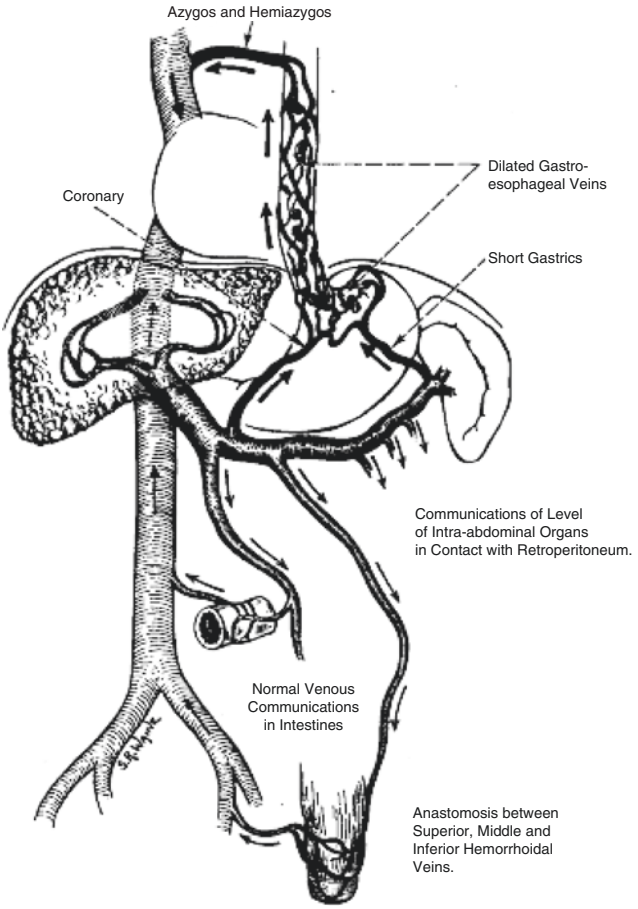


Fig. 12.1 Portosystemic shunts classified by surgeons [1]

Table 12.1 Portosystemic collaterals in 93 cases revealed by percutaneous transhepatic portography (PTP) [2]

Left gastric vein	80	Left inferior phrenic vein	16
Short gastric veins	54	Spleno-gastro-renal collaterals	24
Esophageal veins	82	Para-umbilical vein	27
Para-esophageal veins	27	Inferior mesenteric vein	55
Upper splenic hilum veins	11	Colon veins	22
Lower splenic hilum veins	24	Retroperitoneal veins	28
Right intercostal veins	3	Inferior epigastric veins	8
Left intercostal veins	21	Posterior pancreatico-duodenal vein	25
Diaphragm veins	8	Anterior pancreatico-duodenal vein	11
Mediastinal veins	15	Azygos/hemiazygos veins	18

12.1.3 Method of Obtaining MDCT Images of the Collateral Circulation

Over a period of about 50 s, 100 mL of nonionic contrast media is infused into a peripheral vein with a dedicated injector using a needle thicker than 20 G. Fifty-five seconds after the end of the infusion, during the portal phase, images are obtained from 1-mm-thick slices captured from the chest to the pelvis. Because breath-holding with deep inspiration is required, patients with impaired consciousness cannot be examined.

MDCT should use 16 or more detector rows. In recent years, MDCT with 126 rows has become available, and as a result, shorter imaging times are now possible.

12.1.4 Method of Reconstructing 3DCT Images with the Image Processing Software "ZAIO"

Data stored in pixels are reconstructed using several imaging technologies and visualized as 3DCT images. Several reconstruction methods are available, including volume rendering (VR) and maximum intensity projection (MIP) with colorization. The tracing function for small vessels is also useful to track small and winding veins, but such reconstruction is time-consuming. Blood vessels in 3DCT images should be detected along with the surrounding organs. In order to do so, a single cross section is obtained by multi-planar reconstruction (MPR) as described in the figures below ("Mishuku Hospital Method" [3]). In our implementation of 3DCT, we chose to display the bones along with other structures in order to clarify the spatial orientation. A 3DCT image of esophageal varices and the portal venous

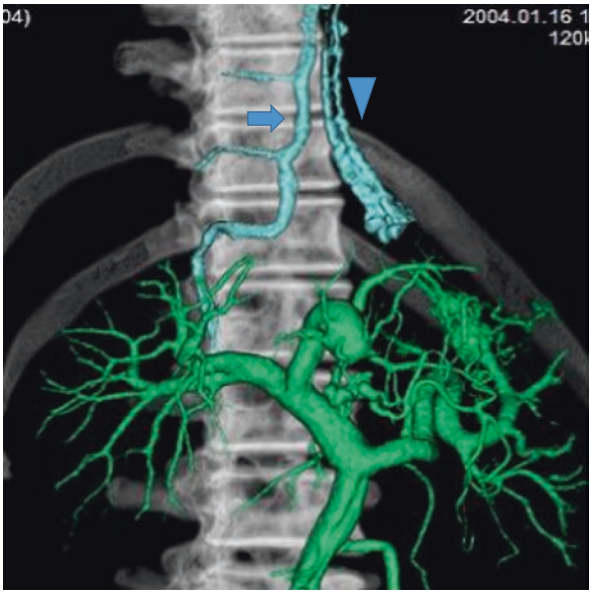


Fig. 12.2 3DCT image of esophageal varices

system is displayed in Fig. 12.2. In the frontal view, esophageal varices can be visualized as tortuous vessels (arrowhead) in front of the vertebra. The blood supply route of the esophageal varices is not clear in Fig. 12.2. The hemiazygos vein (arrow) is visualized near the esophageal varices and is thought to be the drainage pathway. The relative positional relationship between the blood vessels and the stomach or esophagus is difficult to grasp in Fig. 12.2. To clarify this relationship, we resynthesized the MPR image on the same screen (Fig. 12.3). Creating this type of composite image by selecting appropriate cases contributes greatly to attaining an accurate diagnosis.

12.2 Typical Images of the Portal Circulation Collaterals

The collateral circulation revealed by 3DCT is described in this chapter according to the classification of the Japan Society for Portal Hypertension [4], as this system is useful for treatment purposes.

12.2.1 Abdominal Wall Venous System

Paraumbilical veins in the portal venous umbilical region in the left hepatic lobe form shunts extending into veins of the abdominal wall. In the case shown in Fig. 12.4, the abdominal wall veins that act as drainage veins exist on the right and left and can be shallow or deep. A large, deep, tortuous vein on the right abdominal

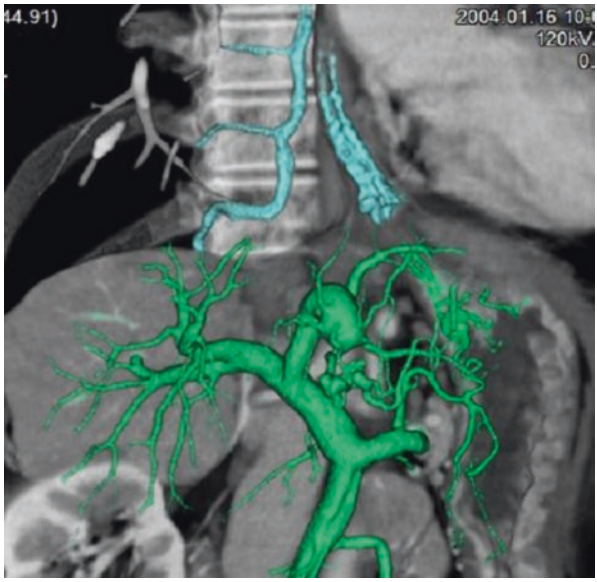


Fig. 12.3 Esophageal varices detected by "Mishuku Hospital Method"

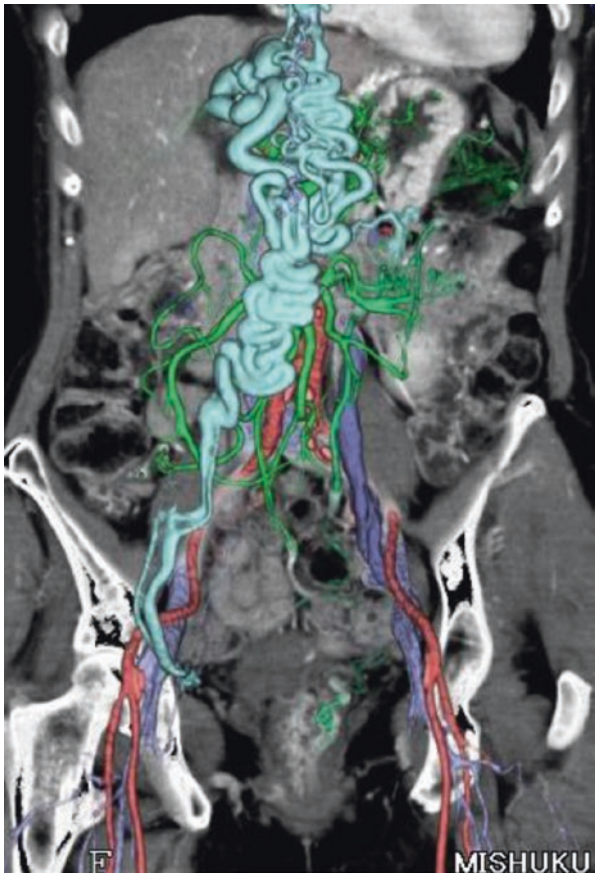


Fig. 12.4 3DCT image of abdominal venous wall collaterals

wall drains into the right common iliac vein and the femoral vein. Since 3DCT permits visualization of vessel diameters, it is useful to estimate blood flow volume. These abdominal wall veins are larger than the mesenteric veins, and therefore occlusion of the collaterals using a catheter temporarily improves hyperammonemia. Drainage through the upper side of the chest wall occurs through the subclavian vein.

12.2.2 Renal Venous System Shunt (Figs. 12.5 and 12.6)

This type of collateral occurs frequently. Gastric varices can be seen when the shunt runs through the gastric mucosa. The posterior gastric vein or the left gastric vein is the supply vein forming gastric varices, through the descending branch of the left inferior phrenic vein and merging into the left adrenal and renal veins. When the collaterals are well-developed, there is a backflow of blood into the splenic vein, leading to hyperammonemia and hepatic encephalopathy. Sometimes, the drainage pathway involves the left gonadal vein.

12.2.3 Azygos Venous System Shunt

The most frequent type of collateral is the azygos venous system shunt. In the case in Fig. 12.7, the left gastric vein joins the hemiazygos vein, forming esophageal varices. Other collateral circulation is not visualized. It should be noted that 3DCT

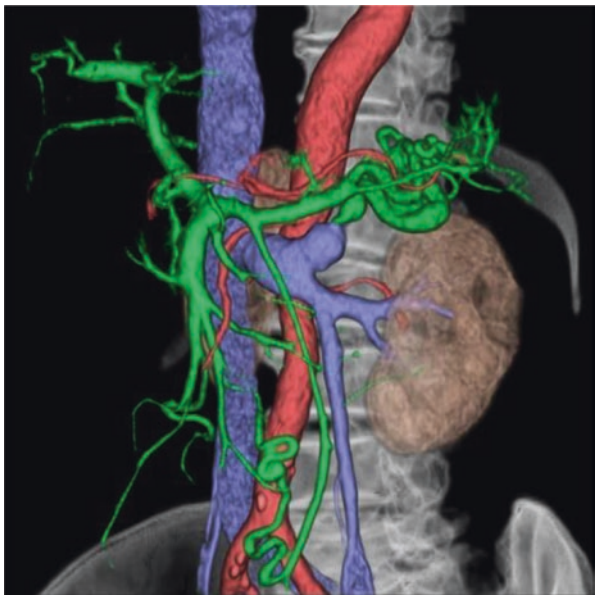


Fig. 12.5 3DCT image of renal venous and inferior mesenteric venous system shunt (frontal view)

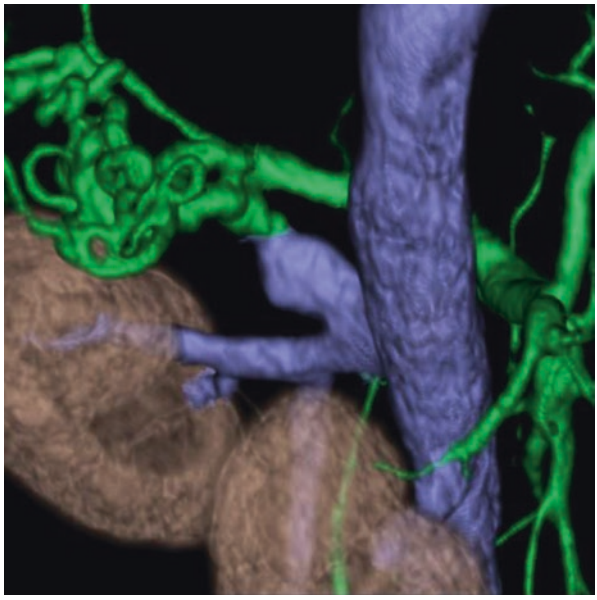


Fig. 12.6 3DCT image of renal venous system shunt (dorsal view)

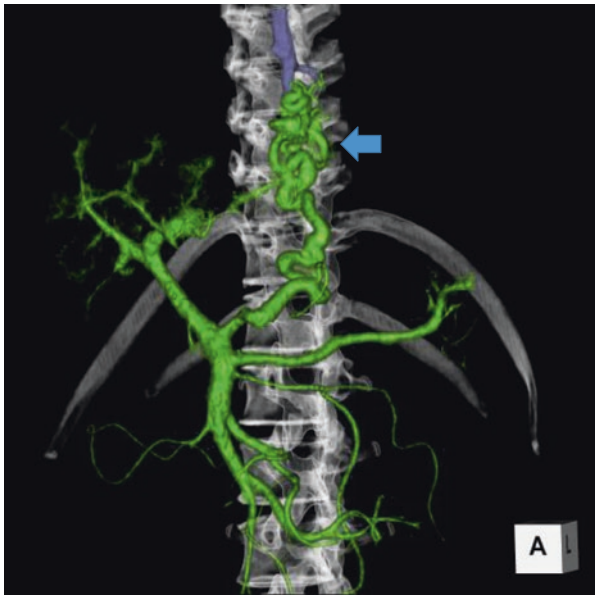


Fig. 12.7 3DCT image of azygos venous system shunt (frontal view)

cannot distinguish collaterals in close proximity to either the inside or outside of the esophageal wall, and conventional CT is necessary in such situations. Thus, the tortuous vessels (arrow) in the case in Fig. 12.7 are paraesophageal veins outside the esophageal wall.

12.2.4 Mesenteric Venous System Shunt

This type of collateral circulation may cause hepatic encephalopathy. Shunts from the inferior mesenteric vein (IMV) are particularly important. In the case shown in Fig. 12.8, there is a well-developed vascular network (arrow) in the retroperitoneal cavity in the lower abdomen. The IMV (arrowhead) is highly dilated. The vein responsible for direct drainage in this case is the inferior vena cava.

In the case in Fig. 12.9, the shunt from the superior mesenteric vein is seen in the right abdomen, shunting into the right gonadal vein, which in turn drains into the proximal portion of the right renal vein.

12.2.5 Diaphragmatic Venous System Shunt

Varicose veins passing through the stomach cardia and flowing into the left inferior phrenic vein are shown in Fig. 12.10. These also run along the upper and dorsal sides of the left hepatic lobe and drain directly into the inferior vena cava. These collaterals sometimes flow into the pericardial or pericardiophrenic veins that empty into the left subclavian vein.

12.2.6 Intrahepatic Shunt (Fig. 12.11)

Large-diameter blood vessels (arrow) in the right hepatic lobe can penetrate the liver. Most portal vein blood flows into the intrahepatic shunt, resulting in narrowing of other branches of the portal vein and subsequent liver atrophy.

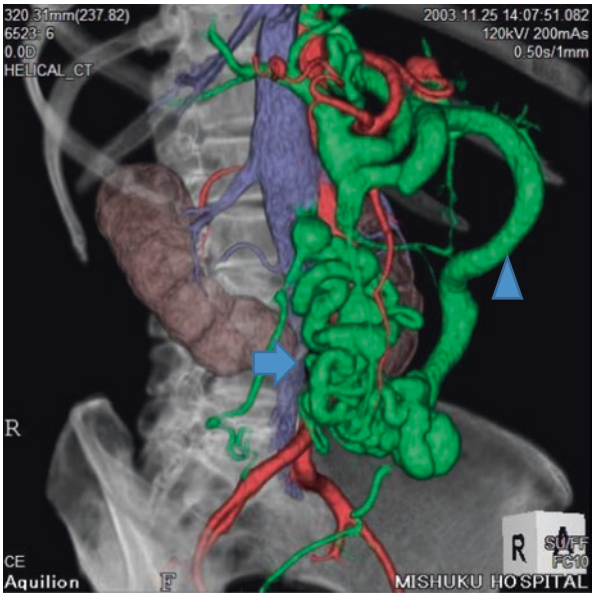


Fig. 12.8 3DCT image of mesenteric venous system shunt

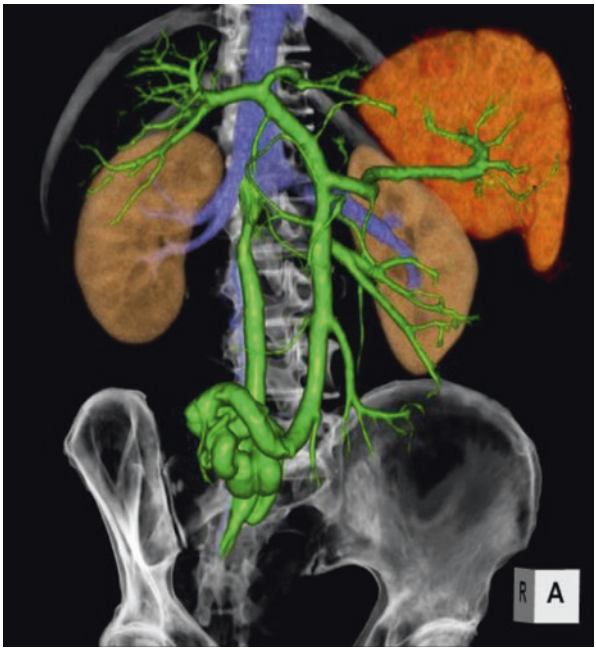


Fig. 12.9 3DCT image of superior mesenteric venous system shunt

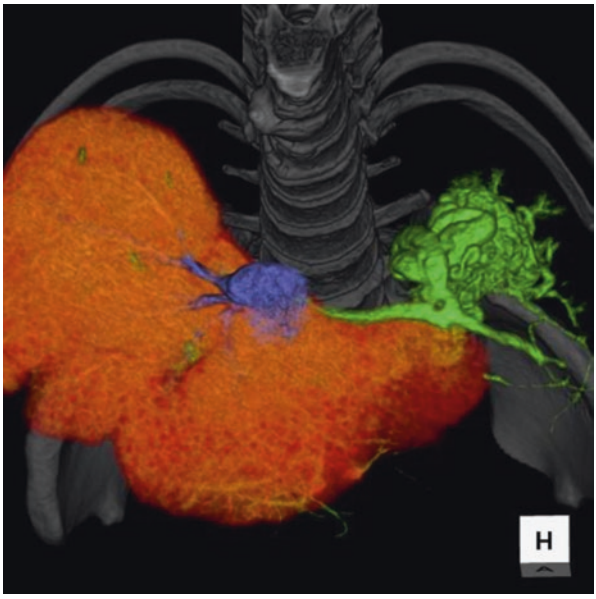


Fig. 12.10 3DCT image of diaphragmatic venous system shunt (cranial view)

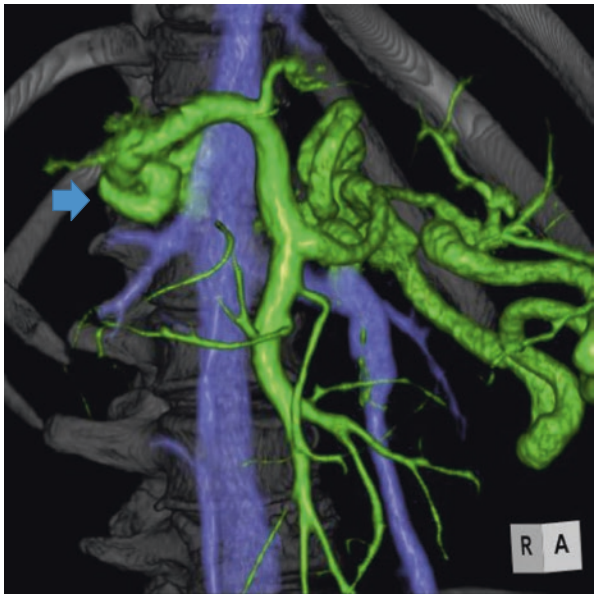


Fig. 12.11 3DCT image of intrahepatic venous shunt

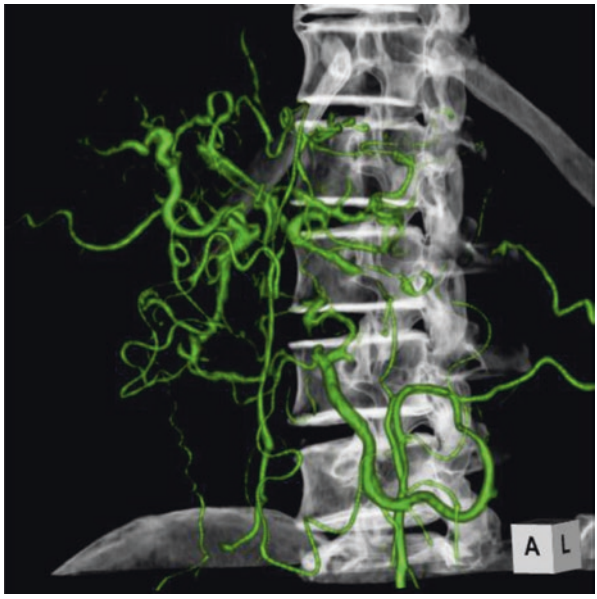


Fig. 12.12 VR reconstruction of 3DCT in case of portal vein thrombosis

12.2.7 Portal Vein Thrombosis

In Fig. 12.12 (VR construction) and Fig. 12.13 (MIP), 3DCT images show diffuse portal vein thrombosis. There are multiple stenotic vessels in the portal and mesenteric venous systems, and main branches such as the portal trunk are obscure. Esophageal varices are present, and portal thrombi are difficult to identify. Using

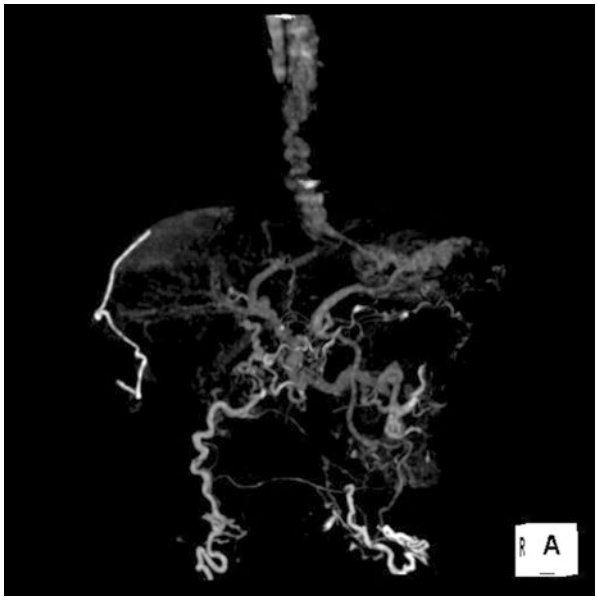


Fig. 12.13 MIP reconstruction of 3DCT in case of portal vein thrombosis

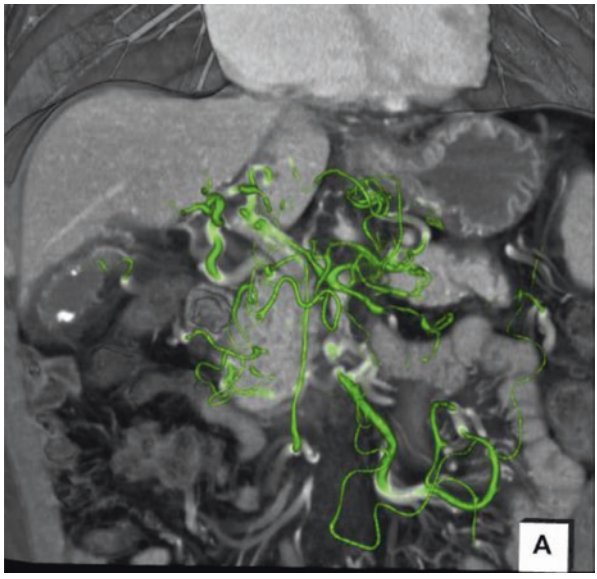


Fig. 12.14 "Mishuku Hospital Method" reconstruction of 3DCT in case of portal vein thrombosis

the "Mishuku Hospital Method" (Fig. 12.14), we can simultaneously display thrombosed veins and venous thrombosis.

12.2.8 Retroperitoneal System Shunt (Fig. 12.15)

In this case, a patient with type B viral cirrhosis had undergone balloon-occluded retrograde transvenous obliteration (B-RTO) for gastric varices 10 years previously. Broadly expanded varicose veins can be visualized in the deep abdominal wall,

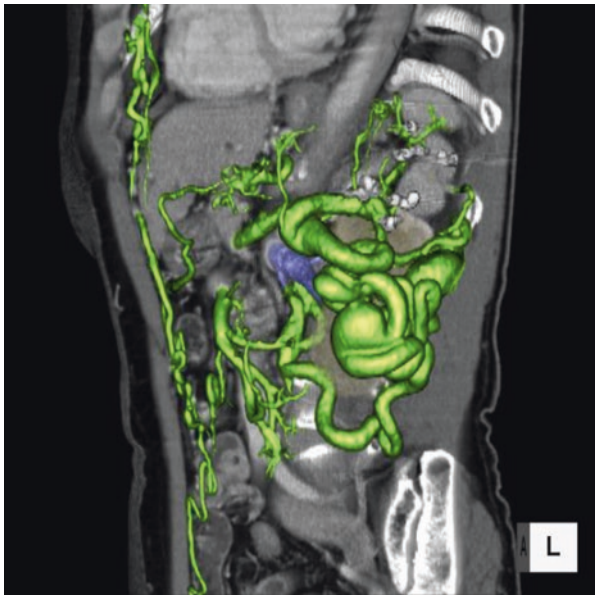


Fig. 12.15 3DCT image of retroperitoneal system shunt (lateral view)

along with retroperitoneal lesions and liver atrophy. The patient experienced repeated episodes of overt hepatic encephalopathy, followed by liver failure. Esophageal and gastric varices are not depicted in this figure. In this case of liver cirrhosis, portosystemic collaterals continued to develop slowly over the course of several years despite narrowing of the main portal branches.

12.2.9 Portopulmonary Venous Shunt (Fig. 12.16)

Paraesophageal veins usually flow into the hemiazygos venous system but sometimes flow directly into the main trunk of the pulmonary vein (portopulmonary venous anastomosis (PPVA); arrow). With these types of collaterals, sclerotherapy may cause cerebral or renal infarction and is therefore contraindicated.

12.3 Incidence of Portosystemic Shunt Detected by 3DCT

A total of 170 consecutive patients with liver cirrhosis who were recruited at Mishuku Hospital were investigated. The frequency of collateral blood vessels to be visualized by MDCT was determined by Dr. Satoshi Nakayama. Collateral pathways were detected in 88 patients (47%). Shunts occurred most frequently in the azygos venous

system (31.8%). Azygos and renal system shunts were observed simultaneously in 15 cases (17.0%) (Fig. 12.17). Figure 12.18 shows a three-shunt system. The details and incidence of these multiple portosystemic shunts are shown in Table 12.2.

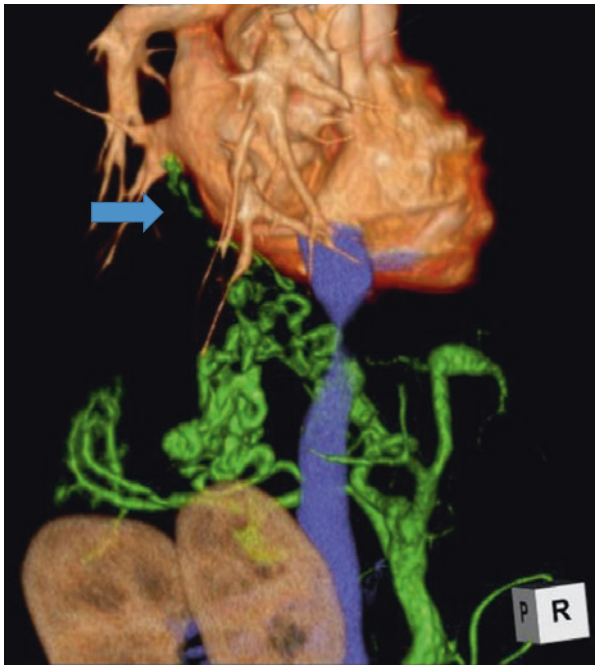


Fig. 12.16 3DCT image of portopulmonary venous shunt (dorsal view)

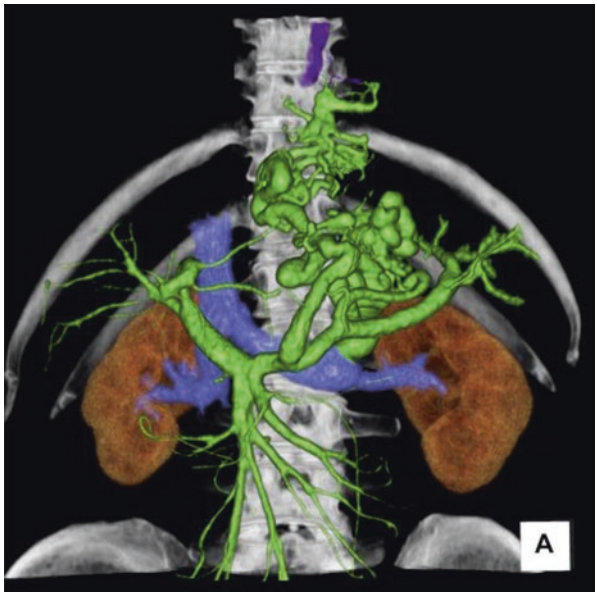


Fig. 12.17 3DCT image of azygos and renal venous system shunts

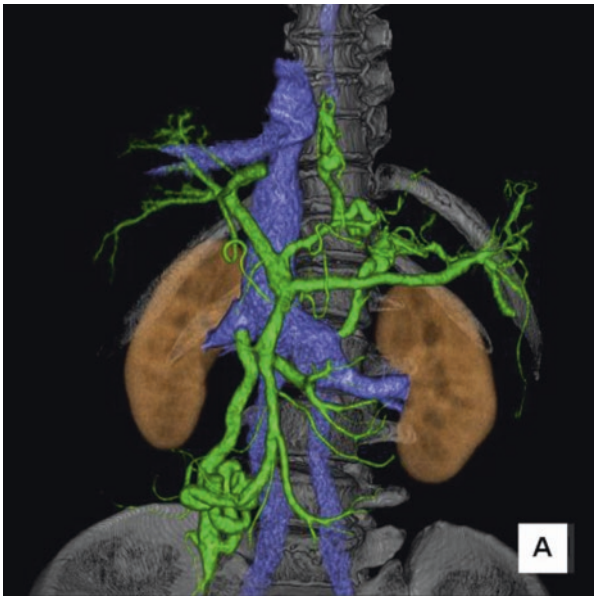


Fig. 12.18 3DCT image of azygos, renal, and mesenteric venous system shunts

Table 12.2 Summary of portosystemic shunt revealed by 3DCT (170 cirrhotics)

Anatomical location of shunts	*n*	Incidence (%)
Abdominal wall venous system shunt only	2	2.3
Renal venous system shunt only	16	18.2
Azygous venous system shunt only	28	31.8
Mesenteric venous system shunt only	4	4.5
Azygous shunt + Abdominal wall shunt	5	5.7
Azygous shunt + Renal shunt	15	17.0
Azygous shunt + Phrenic venous system shunt	1	1.1
Azygous shunt + Mesenteric shunt	2	2.3
Renal shunt + Mesenteric shunt	2	2.3
Renal shunt + Phrenic shunt	2	2.3
Renal shunt + Others	2	2.3
Azygous shunt + Renal shunt + Abdominal wall shunt	2	2.3
Azygous shunt + Renal shunt + Phrenic shunt	2	2.3
Azygous shunt + Renal shunt + Mesenteric shunt	2	2.3
Azygous shunt + Abdominal wall shunt + Mesenteric shunt	2	2.3
Renal shunt + Mesenteric shunt + Mesenteric shunt	1	1.1
Total	88	100

References

1. Rousselot LM, Moreno AH, Panke WF. Studies on portal hypertension. Ann Surg. 1959;150:384–410.
2. Hoevels J, Lunderquist A, Tylen U, Simert G. Portosystemic collaterals in cirrhosis of the liver. Acta Radiol Diagn. 1979;20:86555–795835.
3. Yamana D, Yuba K, Suzuki K, et al. Clinical application of hepatic portal vein 3D image using MDCT-presentation of objective image display (Mishuku Hospital Method). Kyosei Med J. 2006;55:228–32. (in Japanese).
4. The Japan Society for Portal Hypertension. The general rules for study of portal hypertension. 3rd ed. Tokyo: KANEHARA and Co.; 2013. (in Japanese).

Chapter 13
Portal Vein Hemodynamics: MR Imaging and MR Angiography

Satoshi Saitoh and Tatsuya Hatashi

Abstract Magnetic resonance imaging (MRI) is a noninvasive imaging method that is useful for evaluating the state of portal hypertension and the portal collateral vessels. Liver and spleen stiffness can be assessed means of MR elastography, and their stiffness makes it possible to predict the occurrence of esophageal varices. Recently, non-contrast-enhanced MR angiography (NCE-MRA) has been applied to the abdominal region, and selective imaging of the hepatic artery, hepatic vein, or portal vein has become possible in the liver. NCE-MRA enables us to understand the blood flow of the portal collateral circulation. Furthermore, multiple shunts can be detected at the same time. NCE-MRA is a potentially useful method for screening in patients with portal hypertension due to its invasiveness. In contrast-enhanced 3D-CT, as both the arteries and veins are displayed, it takes time differentiating arteries from veins. In contrast, selective vessel imaging is possible with NCE-MRA. Thus, acquiring a 3D image is easier with NCE-MRA than with CT.

Keywords MR elastography · MR angiography · Portal hypertension · Spin labeling

13.1 Introduction

Magnetic resonance imaging (MRI) is a noninvasive imaging method that can be applied to the entire body for better readability. Recently, MRI has been used for the imaging and diagnosis of gastroesophageal varices and portal hypertension.

S. Saitoh (✉)
Department of Hepatology, Toranomon Hospital, Tokyo, Japan
e-mail: sa3110@f2.dion.ne.jp

T. Hatashi
Graduate School of Medical Technology, Teikyo University, Tokyo, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_13

Moreover, liver MR elastography (MRE) is a method used to quantify the level of elasticity or stiffness of the liver and has been developed to achieve a noninvasive assessment of liver cirrhosis or fibrosis. A vibration device is needed to generate mechanical waves in the liver, and the speed of these waves differs depending on the stiffness of the tissue. These waves provide magnetic phase information via a special MRE pulse sequence with synchronized motion encoding gradients and are presented as wave images [1]. Subsequently, the elastogram is obtained by processing the wave information. The stiffness acquired by the MRE is useful as a noninvasive diagnosis of hepatic fibrosis staging [2]. Furthermore, MRE can be applied to the spleen and used to predict the presence of esophageal varices in patients with portal hypertension [3] (Fig. 13.1).

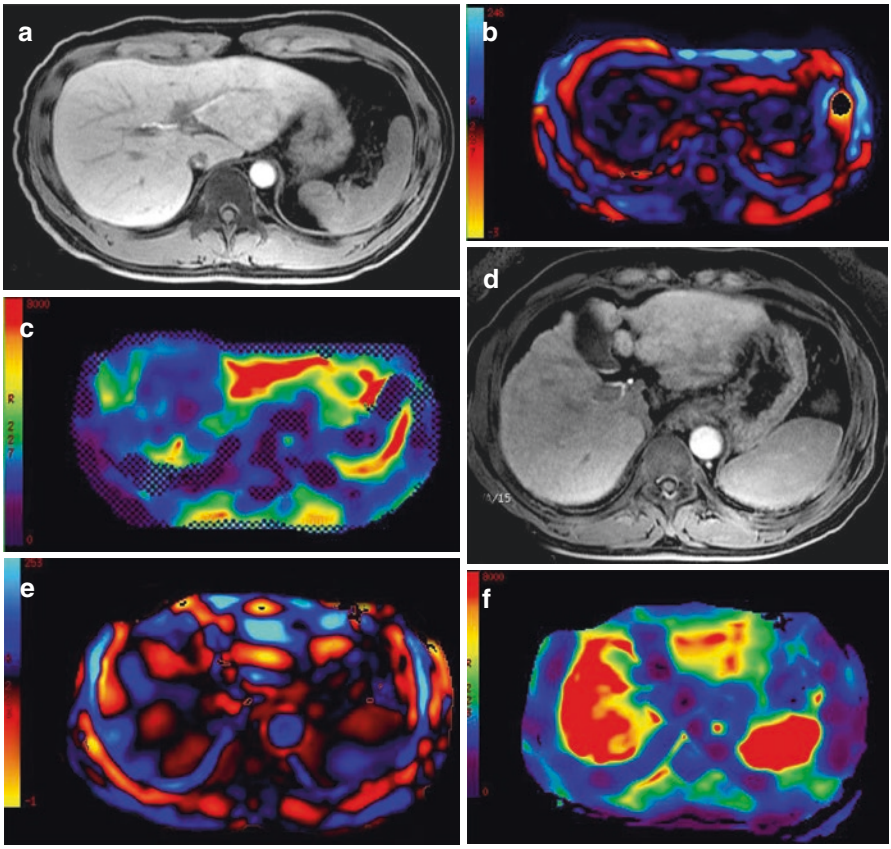


Fig. 13.1 MR elastography. (**a**) EOB-MRI, (**b**) wave image, and (**c**) elastogram of chronic hepatitis type C without esophageal varices. The liver stiffness was 2.1 kPa, and the spleen stiffness was 5.7 kPa. (**d**) EOB-MRI, (**e**) wave image, and (**f**) elastogram of cirrhosis type C with esophageal varices. The liver stiffness was 6.7 kPa, and spleen stiffness was 13.2 kPa. Elevation of the spleen stiffness suggested portal hypertension

For the imaging of portal collateral circulations in patients with portal hypertension, gadolinium (Gd) contrast-enhanced MR angiography (MRA) has been performed. The merits of contrast-enhanced MRA include the capability to provide images within a short period of time and its technical ease of performance. In addition, a large amount of Gd contrast media is used to obtain contrast between vessels and other structures, which results in good quality of the images. However, at present, Gd contrast material is considered to cause nephrogenic systemic fibrosis (NSF) in patients with kidney failure. In addition, Gd contrast media cannot prevent the enhancement of the portal vein, as well as other arteries or veins, leading to poor evaluation in portal collateral circulations. Thus, if any contrast medium is used, the contrast-enhanced CT (CE-CT) appears to be more appropriate than a contrast-enhanced MRI. In addition, non-contrast-enhanced MRA (NCE-MRA) has been widely used in the brain; there is no associated exposure to X-rays or adverse reactions to the contrast medium using this method. Recently, NCE-MRA has been applied to the abdominal region, and selective imaging of the hepatic artery, hepatic vein, or portal vein is possible in the liver. While a CE-CT or MRI is difficult to repeat due to its invasiveness if the acquired image is poor, NCE-MRA is repeatable. In this study, we sought to evaluate NCE-MRA imaging of the portal collateral circulation in patients with portal hypertension.

13.2 Methods and Merit of Spin Labeling MRA

13.2.1 Spin Labeling Techniques

For the selective imaging of the vessels within the portal vein system, spin labeling MRA is used. This technique uses radio-frequency (RF) pulses, such as an inversion recovery (IR) pulse, to magnetically tag protons [4]. Spin labeling techniques consist of the flow-in and the flow-out methods [5]. In the flow-in method, a selective IR pulse is used to suppress background signaling in the region of interest (ROI), and blood protons which enter the ROI are presented as bright blood. In contrast, in the flow-out method, a nonselective IR pulse is used to suppress the entire background signals regardless of the location. Subsequently, a selective IR pulse is used to restore the protons in the targeted vessels. A balanced steady-state free precession (bSSFP) sequence or fast spin echo sequence is used for the spin labeling MRA.

13.2.2 Features of Various Spin Labeling Techniques

The bSSFP sequences are named, respectively, by each vendor as follows: FIESTA (GE), True FISP (Siemens), True SSFP (Toshiba), and balanced FFE (Philips). Additionally, the spin labeling techniques are also named by each company as

follows: Enhance (GE), NATIVE (Siemens), Time-SLIP (Toshiba), and RAVEL (Philips).

Two examples of the spin labeling technique for the imaging of portal collateral circulation are indicated in Fig. 13.2 which presents the image using True FISP with a spin labeling pulse (IR pulse). The IR pulse is located within the liver and heart to suppress background and artery signals. In this way, the protons in the portal vein which flow into the liver can be imaged as bright blood. The other figure (Fig. 13.2b) presents the image using Inhance 3D Inflow IR or NATIVE-True FISP. Under this method, (1) a nonselective IR pulse is used to suppress all background signaling regardless of location, and (2) a selective IR pulse is used to restore the protons in the superior and inferior mesenteric veins as well as the splenic vein which then flow into the portal vein. Then, after magnetically fresh protons flow into the liver, the imaging is performed. In this way, the vessels of the portal vein system can be selectively imaged.

13.2.3 Fusion Image

If a bSSFP sequence is used without a tag pulse (IR pulse), both the portal vein and other arteries and veins are imaged. Thus, the spin labeling technique is required for selective vessel imaging and can also be applied to selective hepatic artery imaging (Figs. 13.3 and 13.4). Therefore, the individual images of the portal vein and hepatic artery can be fused.

13.2.4 Features of NCE-MRA Compared with CE-CT

MRA is not applicable for patients with a cardiac pacemaker, a specific metallic implant, or claustrophobia. In CE-CT, high spatial resolution and wide range imaging in a short time have been made possible by multidetector helical CT scanning. Thus, in dynamic CT, the portal vein system can be imaged during the portal venous phase. While NCE-MRA is inferior to CE-CT for spatial and time resolution, the method does not require contrast media, and there is no associated exposure to X-rays. Thus, patients with kidney failure can undergo NCE-MRA. Furthermore, although the lumbar vein which runs between vertebral bodies is difficult to separate from bone using CE-CT, NCE-MRA achieves favorable imaging of such a vein. The imaging of tiny vessels is difficult; however, it is possible to grasp portal collateral circulations which can run in all directions by NCE-MRA.

As NCE-MRA is performed within approximately 5 min with respiratory gating, uneven breathing could lead to motion artifacts that cannot be eliminated using motion correction. For good imaging quality, some devices (e.g., an abdominal belt) are required to stabilize the respiratory response or to fix coils.

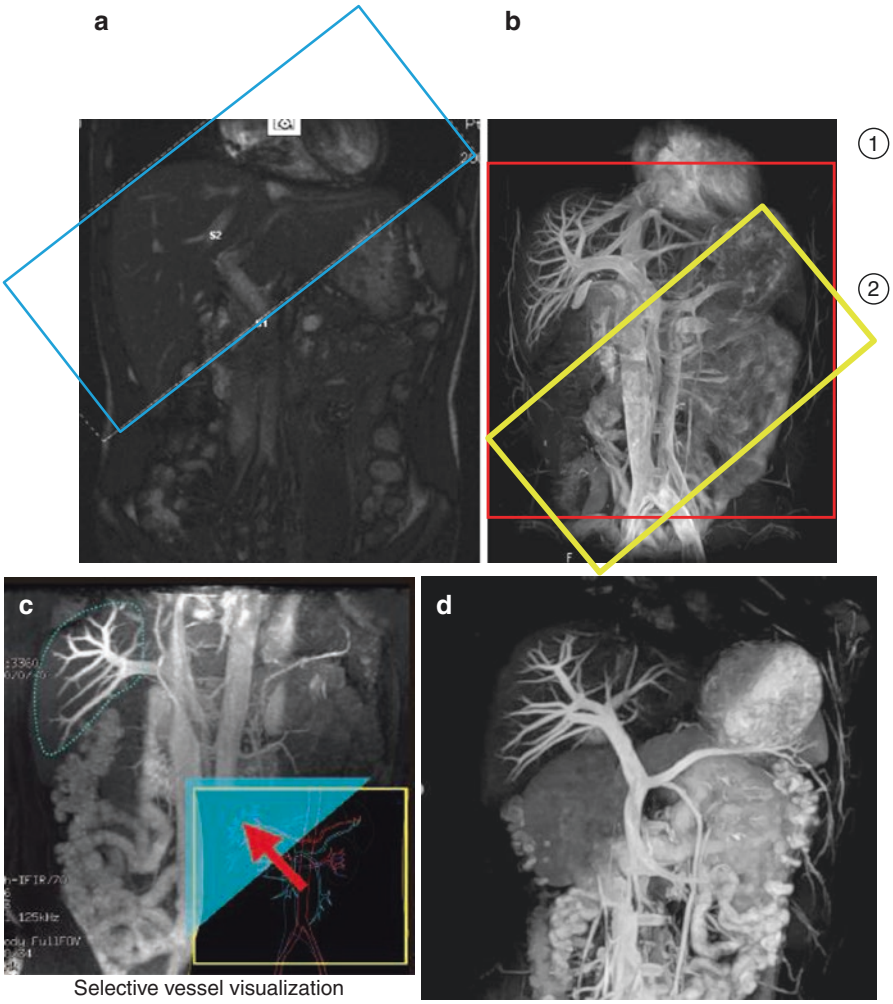


Fig. 13.2 The principle of True SSFP with a spin labeling pulse (**a**) and NATIVE-True FISP (**b**) for imaging the portal vein (**c**). Inhance 3D Inflow IR (**d**) for imaging of the portal vein spin labeling pulse. (**a**) Single IR pulse (within the blue line) is located in the liver and heart to suppress background and artery signals. Next, the scan is performed after the set delay time passes. Within the delay time, the magnetically fresh protons flow into the liver portal vein (Vantage 1.5T Toshiba). (**b**) Double IR pulses are used. ① A nonselective IR pulse is used to suppress the total background signaling, regardless of location, and ② a selective IR pulse is used to restore the protons in the vessels which flow into the portal vein (superior and inferior mesenteric veins, as well as the splenic vein). After the magnetically fresh protons flow into the liver, the scan is performed (Magnetom Avanto 1.5T Siemens). The principle of True SSFP with (**c**) Inhance 3D Inflow IR (**d**) for imaging of the portal vein spin labeling pulse. (**c**) A single IR pulse is located in the liver and heart to suppress background and artery signals. The scan is performed after the set delay time passes. Within the delay time, the magnetically fresh protons flow into the portal vein of the liver. (**d**) Double IR pulses are used. ① A nonselective IR pulse is used to suppress the entire background signaling, regardless of location, and ② a selective IR pulse is used to restore the protons in the vessels which flow into the portal vein (superior and inferior mesenteric veins, as well as splenic vein). After the magnetically fresh protons flow into the liver, the scan is performed (1.5T Optima MR 360 is used. The images are provided by GE)

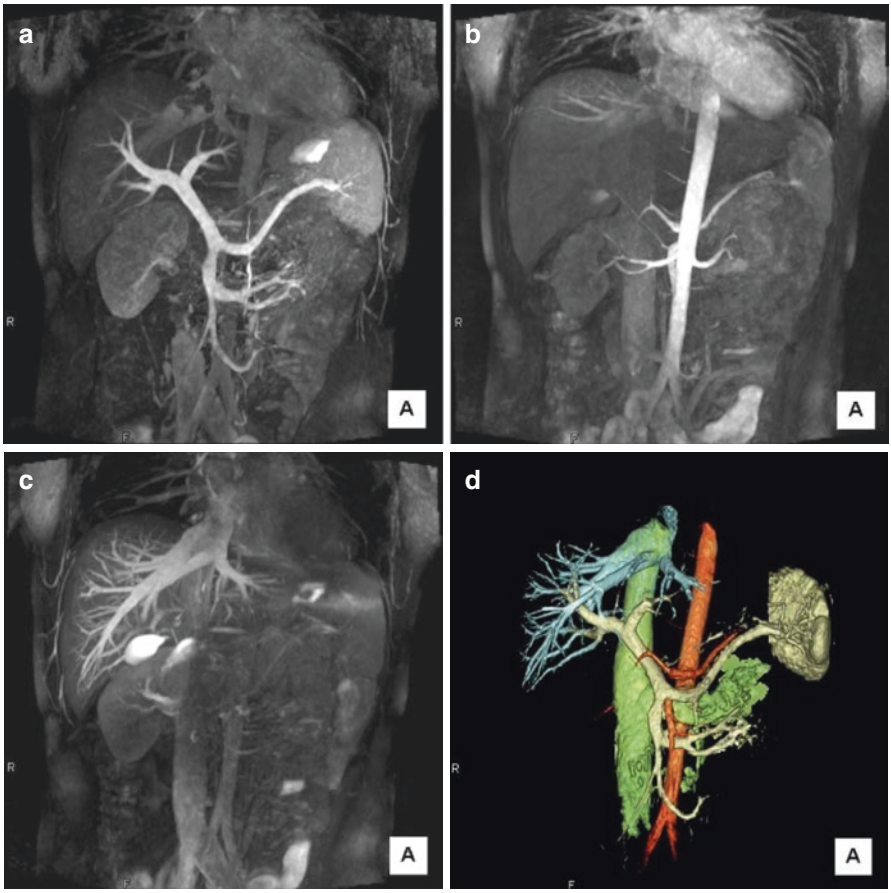


Fig. 13.3 The fusion image of the portal vein and hepatic artery with True SSFP with a spin labeling pulse (NATIVE-True FISP, Siemens). The separate image of (**a**) the portal vein and (**b**) hepatic artery that is scanned by NCE-MRA. (**c**) The hepatic vein and (**d**) the fusion image of the portal vein and hepatic artery. The blue vessel is a portal vein and the red vessel is an artery

13.3 Imaging of Intra- and Extrahepatic Portal Vein Using the Spin Labeling Method

13.3.1 Imaging of the Intrahepatic Portal Vein

At our institution, the first-, second-, and third-order intrahepatic portal veins can be imaged in patients with a normal liver or chronic hepatitis (Fig. 13.4.). In patients with cirrhosis, although the second-order intrahepatic portal vein was imaged in all patients, the third-order intrahepatic portal vein was imaged in 90–95% of patients with Child-Pugh A and in only 50–80% of patients with Child-Pugh B or C (Figs. 13.5 and 13.6). These findings are consistent with a previous study [6].

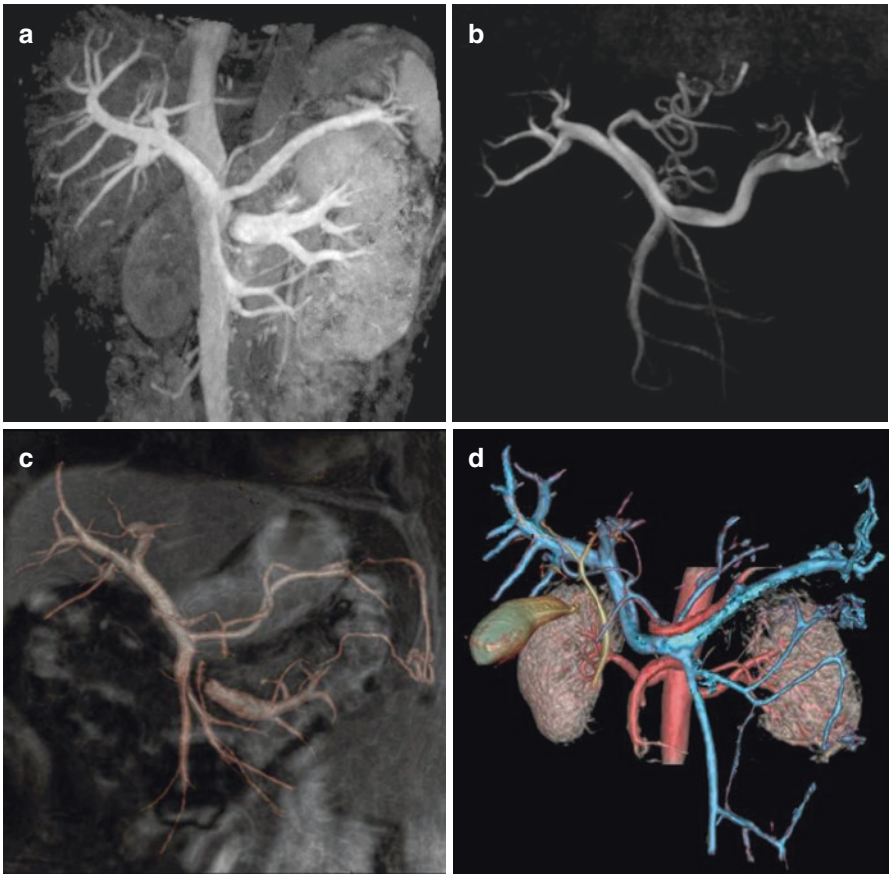


Fig. 13.4 The image of NCE-MRA (NATIVE-True FISP) in a patient without portal hypertension (**a**). Branches of the portal veins are detected even in the peripheral vessels. The left gastric vein runs from the origin portion of the portal vein. The portal collateral circulation is not detected. (**b**) Inhance Inflow IR MIP. Inhance 3D Velocity (3.0T, GE). (**c**) Inhance Inflow IR-Fusion and (**d**) Inhance Inflow IR + MRCP VR. Courtesy of JA Onomichi General Hospital

13.3.2 Imaging of the Extrahepatic Portal Vein

Imaging of the extrahepatic portal vein (main portal vein, splenic vein, and superior mesenteric vein) could be possible in patients with a normal liver or chronic hepatitis, except for patients who have undergone a gastrectomy. Regarding portal vein thrombosis, although the original images could be used to assess thrombosis, the identification of thrombosis was difficult in the maximum intensity projection (MIP) images.

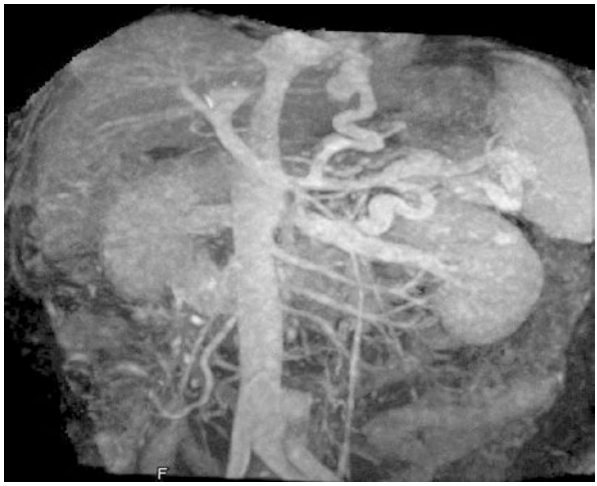


Fig. 13.5 The image of the gastroesophageal varices of the left gastric vein and left renal vein shunt in patients with decompensated cirrhosis (Child-Pugh C). Various shunts can be detected by NCE-MAR. The third-order intrahepatic portal veins are imaged with difficulty

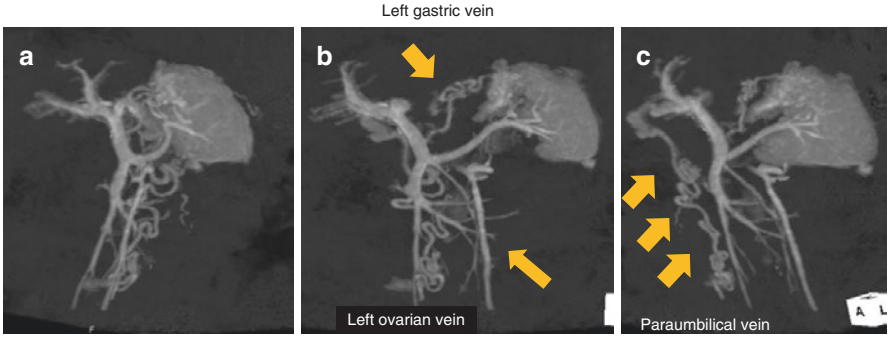


Fig. 13.6 The imaging of the portosystemic shunt. (**a**) The left gonadal vein which descends from the left renal vein and the inferior mesenteric vein can be detected. The vessel which ascends to the back side is the left lumbar vein. (**b**) is the axial image for a patient who has variable portal collateral circulation. The paraumbilical vein, the lumbar vein, and the shunt which surfaces from the posterior segment. (**c**) is the coronal image from the same patient. A duodenal varix from the splenic vein is detected. There are no clear symptoms of hepatic encephalopathy in the patient with a blood ammonia level of 99 ng/mL

13.4 Imaging of Extrahepatic Portal Collateral Circulation Using the Spin Labeling Method

13.4.1 Imaging of Esophageal Varices

NCE-MRA enables us to understand the blood flow of the portal collateral circulation. Furthermore, multiple shunts can be detected at the same time. When observing esophageal varices, we cannot acquire such detailed findings (e.g., red color signs) by NCE-MRA by endoscopy. However, the entire aspect of the widespread shunt, which

cannot be evaluated by endoscopy, can be obtained. Therefore, spin labeling MRA may be helpful when deciding on a therapeutic strategy. Esophageal varices are thought to be from the left gastric vein. As shown in Fig. 13.6, we can image the left gastric vein from the main trunk of portal vein. Thus, it is useful to use NCE-MRA before and after the treatment of esophageal varices to evaluate the therapeutic effect.

13.4.2 Imaging of Gastric Varices

Gastric varices are supplied with blood from various vessels, including the short gastric vein, posterior gastric vein, and left gastric vein (Figs. 13.7, 13.8, and 13.9). Moreover, the left renal vein is the primary drainage vessel of the gastric varix. Figure 13.8 presents images of gastric varices. Although the gastric varices are not large at the basal surface of the stomach, the varices expand under the basal surface. In an another example by 3D CE-CT, the drainage vein is not the left gastric vein (Fig. 13.9).

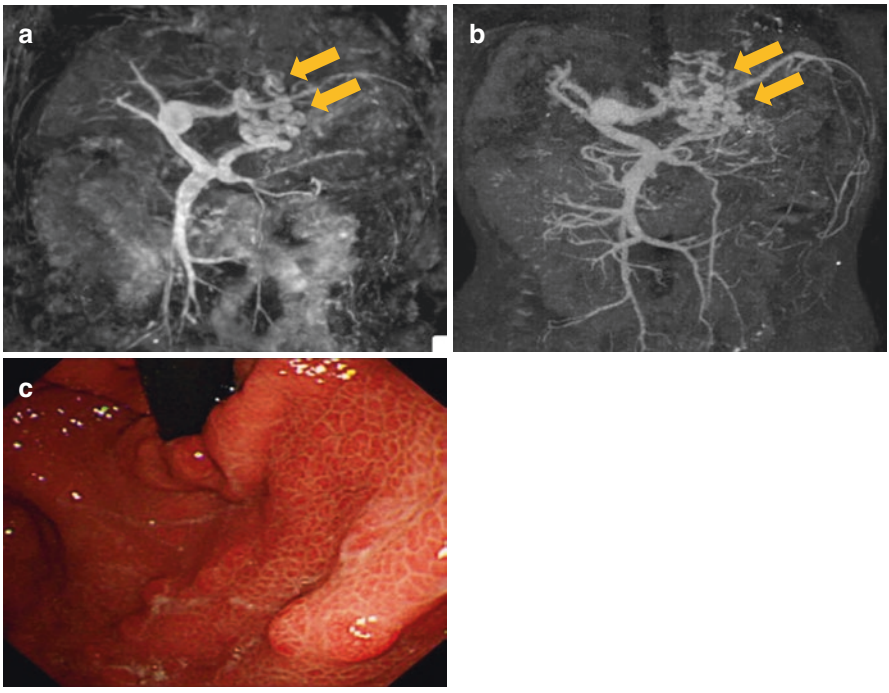


Fig. 13.7 (**a**) The image obtained via NCE-MRA using True SSFP with NATIVE. In the gastric varices, the blood is supplied from a left gastric vein. As shown in the image at another angle, the short gastric vein also connects with the varices. The arrows show the gastric varices. (**b**) The image by CE-CT. Although the gastric varices are clearly imaged, the left gastric vein is vague. The arrows show the gastric varices. (**c**) The image by endoscopy. The length of the gastric varices is low and does not need to be treated

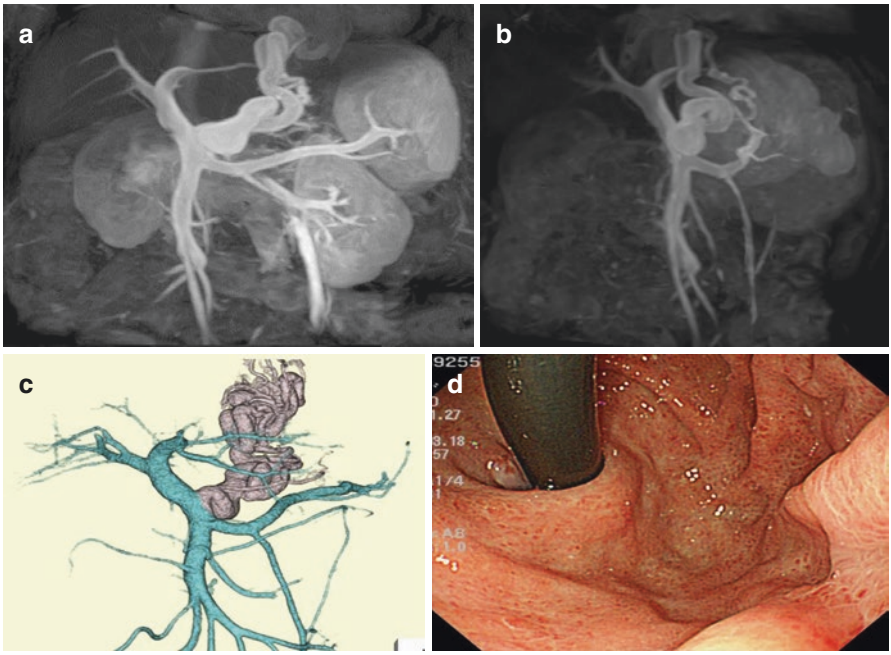


Fig. 13.8 The image of the gastric varices. (**a**) The image of the left gastric vein acquired by a True SSFP with Time-SLIP pulse. The varices are derived from the posterior gastric vein and short gastric vein. The gastrorenal shunt and splenorenal shunt are made. The extension of the inferior mesenteric vein and left gonadal vein can be detected (MIP image). (**b**) MIP image, (**c**) volume rendering, (**d**) endoscopic image

The left renal vein shunt is diverse (Figs. 13.7 and 13.8). As shown in the figure, some of the shunts are connected with the lower vessel rather than a renal vein. In particular, the left gastric venous shunt, inferior mesenteric venous shunt, and left gonadal vein are complicated [7]. If there are more than three shunts, the blood ammonia levels increase, which may lead to hepatic encephalopathy.

13.4.3 Detection Rate of Portosystemic Shunts

Table 13.1 shows the detection rates of portosystemic shunts by NCE-MRA using CE-CT as the reference standard. The detection rate of the paraumbilical vein was much lower by NCE-MRA because the paraumbilical vein was out of the imaging range in this study. At our institution, because the scan time of MRA is set at approximately 5 min, the abdominal wall is outside of the imaging area; however, if the scan time is set longer, the paraumbilical vein can be visualized. Although small vessels are difficult to detect in patients with irregular respiration, large shunts can be imaged.

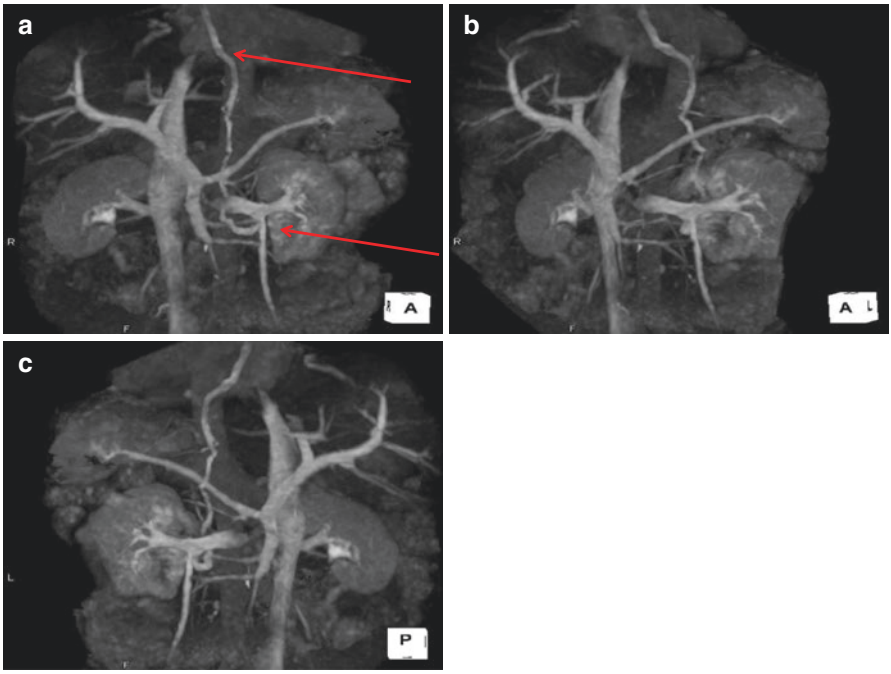


Fig. 13.9 The left lumbar vein shunt. (a) The left lumbar vein shunt and the left gonadal vein shunt. The upper arrow represents the left lumbar vein, and the lower arrow shows the left gonadal vein (coronal view). (**b**) The 3D image of the left lumbar vein shunt (oblique view). (**c**) The shunt branches from the left gonadal vein and ascends (back side view)

Table 13.1 Detection rate of portosystemic shunts

Shunt	Number of detected shunts
Left renal vein shunt	67/75 (89%)
Gastrorenal shunt	21/21 (100%)
Splenorenal shunt	24/24 (100%)
Inferior mesenteric shunt	10/10 (100%)
Left gonadal or ovarian shunt	28/28 (100%)
Paraumbilical vein shunt	15/25 (60%)

Data are expressed as the number of detected portosystemic shunts by NCE-MRA/CE-CT with the percentages in parentheses

For shunts that could not be detected with CE-CT imaging was possible using NCE-MRA. The left lumbar vein branches downward from the left renal vein and runs backward (Fig. 13.9). The vein then threads upward around the vertebral body and joins the hemiazygos vein. A tiny left lumbar vein could be detected in a healthy person, and a ticked lumbar vein could be clearly imaged in patients with portal hypertension. Moreover, the left lumbar vein needs to be treated using

balloon-occluded retrograde transvenous obliteration (BRTO), for which interventional treatment is performed via the medium of the left renal vein. The vein is difficult to differentiate from the vertebral body using three-dimensional CT (3D-CT). Although the vein can be detected in axial slices, it is difficult to recognize the entire image.

13.5 Conclusion

NCE-MRA has been widely used as a noninvasive imaging method in the brain. Although 3D-CT using a contrast medium is superior to NCE-MRA in spatial and time resolution, NCE-MRA is a potentially useful method as a screening test for patients with portal hypertension due to its invasiveness. In contrast-enhanced 3D-CT, both the arteries and veins are displayed, and the differentiation of these vessels takes time. In contrast, selective vessel imaging is possible with NCE-MRA. Moreover, acquiring a 3D image is easier with NCE-MRA than with CE-CT. In Japan, a large number of portal hypertension cases are caused by cirrhosis which increases the risk of developing hepatocellular carcinoma. Recently, Gd-EOB-DTPA has been used as a screening test for hepatocellular carcinoma. We recommend including NCE-MRA in the protocol for Gd-EOB-DTPA MRI.

References

1. Venkatesh SK, Yin M, Ehman RL. Magnetic resonance elastography of liver: technique, analysis, and clinical applications. J Magn Reson Imaging. 2013;37:544–55.
2. Yin M, Glaser KJ, Talwalkar JA, et al. Hepatic MR elastography: clinical performance in a series of 1377 consecutive examinations. Radiology. 2016;278:114–24.
3. Talwalkar JA, Yin M, Venkatesh S, et al. Feasibility of in vivo MR elastographic splenic stiffness measurements in the assessment of portal hypertension. AJR Am J Roentgenol. 2009;193:122–7.
4. Miyazaki M, Akahane M. Non-contrast enhanced MR angiography: established techniques. J Magn Reson Imaging. 2012;35:1–19.
5. Furuta A, Isoda H, Yamashita R, et al. Non-contrast-enhanced MR portography with balanced steady-state free-precession sequence and time-spatial labeling inversion pulses: comparison of imaging with flow-in and flow-out methods. J Magn Reson Imaging. 2014;40:583–7.
6. Ito K, Koike S, Shimizu A, et al. Portal venous system: evaluation with unenhanced MR angiography with a single-breath-hold ECG-synchronized 3D half-Fourier fast spin-echo sequence. AJR Am J Roentgenol. 2008;191:550–4.
7. Hoshida Y, Saitoh S, Murashima N, et al. Vaginal variceal hemorrhage in a patient with primary biliary cirrhosis: a case successfully treated by balloon-occluded retrograde transvenous obliteration. AJR. 1999;94:3081–3.

Chapter 14
Endoscopic Varicealography During Endoscopic Injection Sclerotherapy (EVIS)

Fumio Chikamori and Yasuhiro Takase

Abstract Endoscopic varicealography (or varicography) during endoscopic injection sclerotherapy is a retrograde venography as described in Chap. 23 "Takase method" of endoscopic injection sclerotherapy for esophagogastric varices. Excessive injection of 5% ethanolamine oleate with iopamidol (5%EOI) causes portal thrombosis, renal dysfunction, or lung congestion. The flow of the sclerosant is monitored by varicealography. The amount of 5% EOI can be controlled either by visualizing the filling of supply route or visualizing paraesophageal, inferior phrenic, or mediastinal veins.

Keywords Endoscopic varicealography during endoscopic injection sclerotherapy Esophagogastric varices

14.1 Introduction

Contrast radiography for portal collateral pathways is divided into two types: antegrade and retrograde venography.

Percutaneous transhepatic portography (PTP) [1] is an antegrade venography, which provides the most precise information about portal collaterals. However, it is invasive for the patients with liver cirrhosis. On the other hand, arterial portography is safe and less invasive but less precise than PTP. Endoscopic varicealography (or varicography) during endoscopic injection sclerotherapy (EVIS) is a retrograde venography as described in Chap. 23 "Takase method" of endoscopic injection sclerotherapy (EIS) for esophagogastric varices [2].

F. Chikamori (✉)
Department of Surgery, Tano Hospital, Kochi, Japan

Y. Takase
Department of Surgery, Tsukuba Soai Hospital, Ibaraki, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_14

14.2 Vascular Map of the Portal System

Based upon the findings of PTP in 75 patients with esophagogastric varices, we constructed a vascular map of the portal system (Fig. 14.1) [3].

The blood supply routes of esophageal varices are divided into two systems: a major supply route comprised mainly of the left gastric vein (LGV) and a minor supply route comprised of the short gastric vein (SGV). Each of them constitutes a separate system of blood flow, which is independent of the other. The LGV system consists

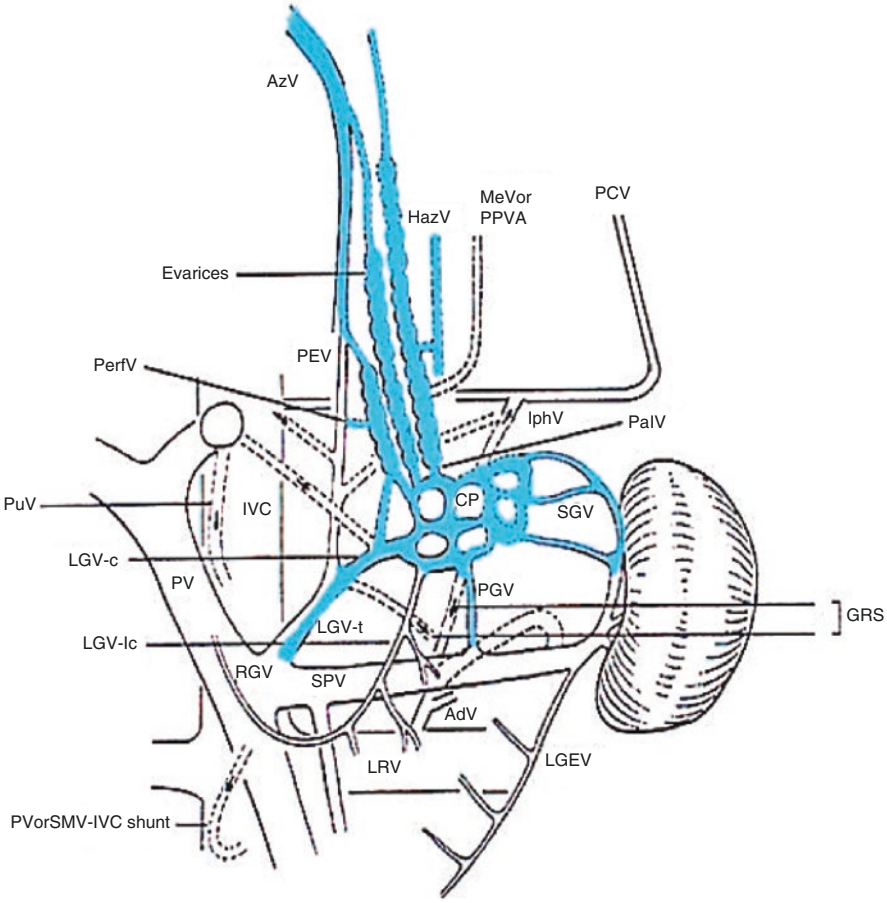


Fig. 14.1 Vascular map for treating esophagogastric varices. *PV* portal vein, *SPV* splenic vein, *IVC* inferior vena cava, *LGV-t* trunk of the left gastric vein, *LGV-c* cardiac branch of the left gastric vein, *LGVlc* lesser curvature branch of the left gastric vein, *PGV* posterior gastric vein, *SGV* short gastric vein, *RGV* right gastric vein, *LGEV* left gastroepiploic vein, *CP* cardiac venous plexus, *PalV* palisade vein, *Evarices* esophageal varices, *PEV* paraesophageal vein, *PerfV* perforating vein, *AzV* azygos vein, *HazV* hemiazygos vein, *MeV or PPVA* mediastinal vein or portopulmonary venous anastomosis, *AdV* adrenal vein, *LRV* left renal vein, *PuV* paraumbilical vein, *IphV* inferior phrenic vein, *GRS* gastrorenal shunt, *PCV* pericardial vein, *PV or SMV-IVC shunt* portal vein or superior mesenteric vein-IVC shunt

of the trunk, cardiac branch and lesser curvature branch of the LGV, and the cardiac venous plexus (CP). The number of trunks in the LGV is sometimes two or more. The SGV system consisted of trunks, the fundic branch of the SGV, and the posterior gastric vein and communicates with the CP. The lesser curvature branch of the LGV communicates with the right gastric vein and the left gastroepiploic vein. The paraesophageal and the inferior phrenic veins are the other blood drainage routes of the LGV.

14.3 Analysis of Blood Supply Routes of Esophageal Varices Comparing EVIS and PTP

14.3.1 Blood Supply Routes of Primary Esophageal Varices

The blood supply routes of primary and recurrent varices in 11 cases of recurrent esophageal varices were analyzed by comparing the EVIS images obtained at EIS using the Takase method initial and repeat EIS with PTP images before and after initial EIS [4].

EVIS at initial EIS [4] showed the vessels of the LGV system, such as the cardiac branch and the CP in all 11 cases with primary esophageal varices. The trunk of the LGV was visible in 73% (8/11) and the posterior gastric vein in 18% (2/11) cases (Figs. 14.2 and 14.3).

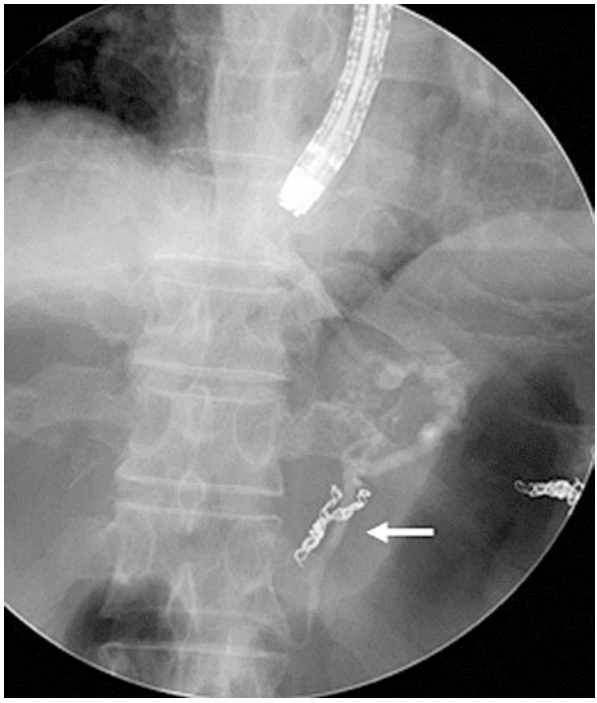


Fig. 14.2 LGV. EVIS showing that the esophageal varices are supplied by the LGV (*arrow*)

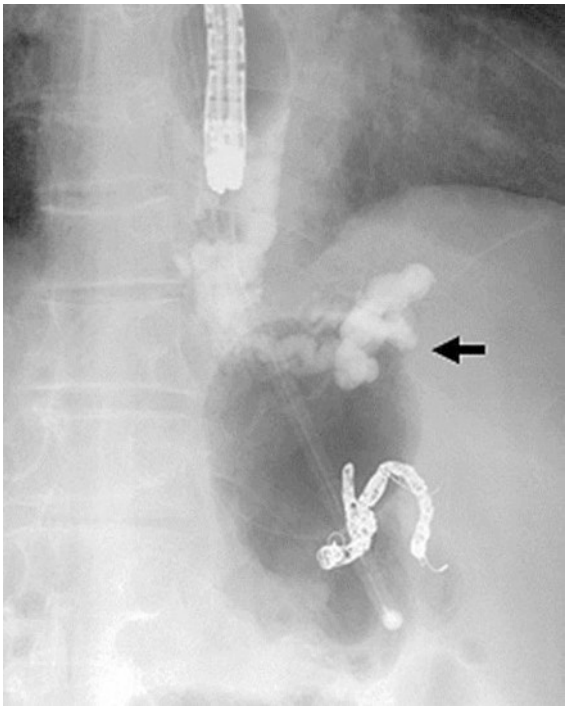


Fig. 14.3 Gastroesophageal varices. EVIS showing esophagogastric varices (*arrow*)

14.3.2 Blood Supply Routes of Recurrent Esophageal Varices After EIS

The blood supply routes of recurrent varices, demonstrated by EVIS, are the vessels of the SGV system, such as the fundic branch of the SGV (Fig. 14.4) or the posterior gastric vein in 82% (9/11) of cases and the partially reformed fine CP in 27% (3/11) of cases [4].

14.3.3 Blood Supply Routes of Esophageal Varices After Total Gastrectomy

Esophagojejunal varices after total gastrectomy are supplied by the branches of the jejunal vein of the arcade of the ascending jejunal limb (Fig. 14.5) [5].

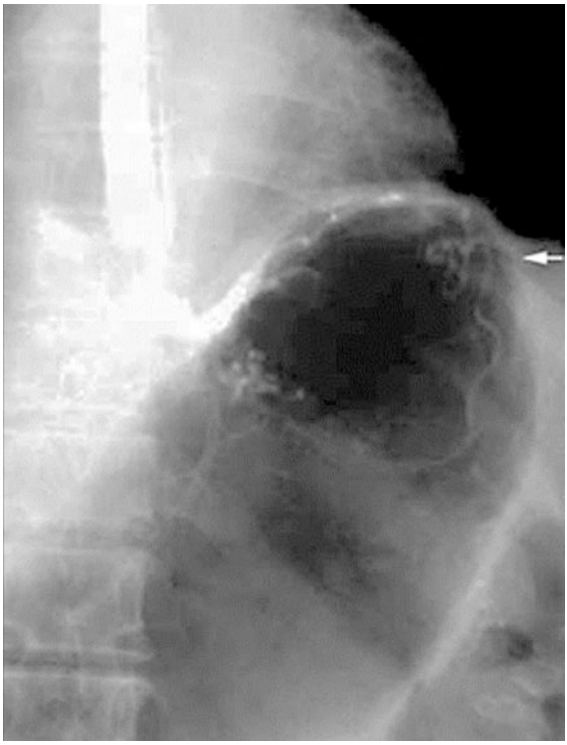


Fig. 14.4 SGV. EVIS showing that the recurrent varices are supplied by the fundic branch of the SGV (*arrow*)

14.4 Usefulness of EVIS

14.4.1 Technical Aspects of EVIS

At the time of EIS, excessive injection of 5% EOI causes portal thrombosis, renal dysfunction, or lung congestion. Therefore, in order to prevent excessive injection of 5% EOI, the flow of the sclerosant is closely monitored by varicealography. The amount of 5% EOI can be controlled either by visualizing the filling of supply routes or by visualizing the paraesophageal (Fig. 14.6), inferior phrenic, or mediastinal veins (Fig. 14.7) [6].

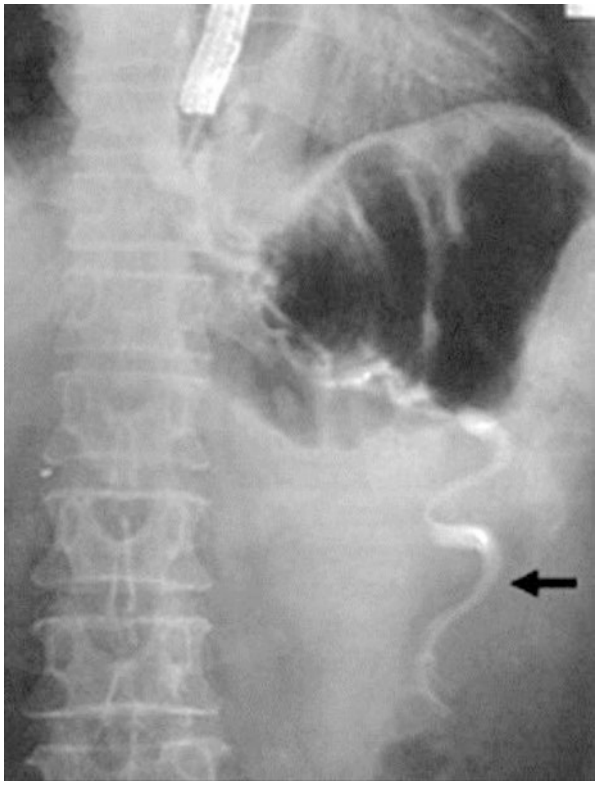


Fig. 14.5 Jejunal vein. EVIS showing that esophageal varices after total gastrectomy are supplied by branches of the jejunal vein of the arcade of the ascending jejunal limb (*arrow*)

14.4.2 Visualization Rate by EVIS for Each Collateral Pathway

Portal collaterals were evaluated using the Takase method in 126 patients with esophageal varices [7]. Analysis of EVIS showed that 52% of collaterals could be visualized for LGV, 48% for CP, 9% for SGV, and 14% for extraesophageal blood drainage routes.

According to our results, we believe that in EIS, a necessary injection dose must be established according to the volume of these visualized blood supply routes varicealography.

Acknowledgments I thank Dr. Niranjan Sharma PhD, Mornington Health Center Dunedin, New Zealand, for helpful comments.

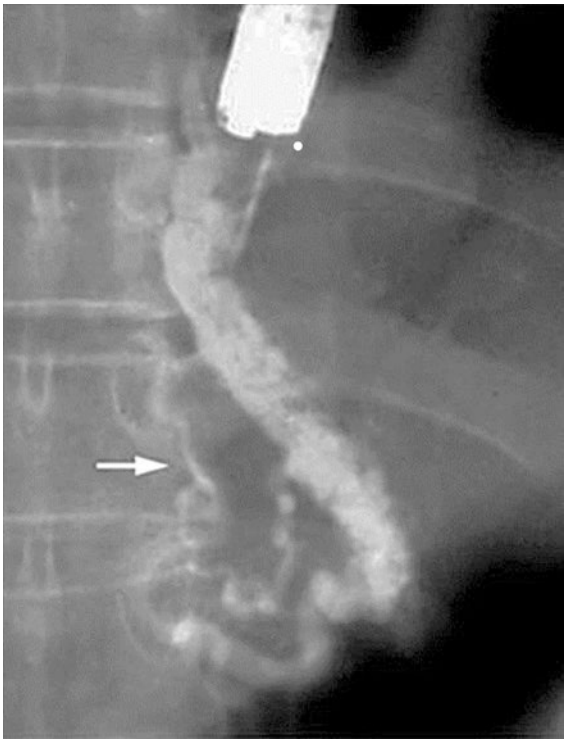


Fig. 14.6 Paraesophageal vein. EVIS showing esophageal varices, cardiac branch of the LGV, and paraesophageal vein (*arrow*)

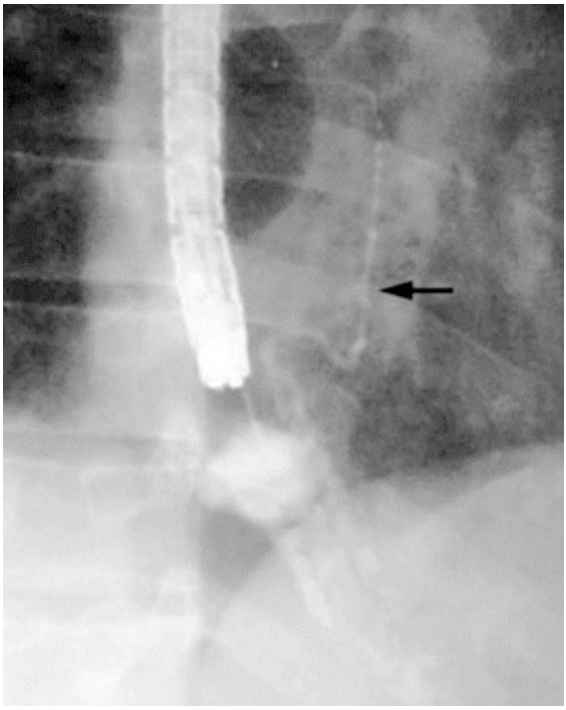


Fig. 14.7 Mediastinal vein. EVIS showing esophageal varices and mediastinal vein (*arrow*)

References

1. Lunderquist A, Vang J. Transhepatic catheterization and obliteration of the coronary vein in patients with portal hypertension and esophageal varices. N Engl J Med. 1974;291:646–9.
2. Takase Y, Shibuya S, Sharma N. Radiological control of injected sclerosant for esophageal varices by endoscopic varicography during injection sclerotherapy. Dis Esophagus. 1990;3:23–32.
3. Chikamori F, Kuniyoshi N, Shibuya S. Takase:Correlation between endoscopic and angiographic findings in patients with esophageal and isolated gastric varices. Dig Surg. 2001;18:176–81.
4. Chikamori F, Nishio S, Kuniyoshi N, Shibuya S, Takase Y. Blood supply routes of recurrent esophageal varices following endoscopic embolization. Dig Surg. 2000;17:17–22.
5. Chikamori F, Aoyagi H, Takagaki T, Sharma N, Shibuya S, Takase Y. Injection sclerotherapy for esophageal varices after total gastrectomy. Case reports of two patients. Dig Endosc. 1992;4:274–80.
6. Chikamori F, Kuniyoshi N, Shibuya S, Takase Y. Short-term portal hemodynamic effects of endoscopic embolization for esophageal varices. Dig Surg. 2000;17:454–8.
7. Chikamori F, Kobayashi Y, Takase Y. Studies on collaterals in portal hypertension based on endoscopic varicealography (in Japanese). Gastroenterol Endosc. 1987;29:1695–701.

Chapter 15
Angiographic Evaluation of Portal Hypertension

Shozo Hirota, Yasukazu Kako, and Kaoru Kobayashi

Abstract Recent advances in CT (computed tomography) scanning have made it possible to obtain clear 3D depictions of the vascular system. But angiography of the portal vein system is essential in order to grasp the hemodynamics of portal hypertension or to perform interventional radiology of varices. Angiography systems are now being equipped with C-arm cone-beam CT or gantry-type CT scanners. Portography is obtained during portal phase of superior mesenteric arteriography using a vasodilator or by angiography via a catheter inserted directly into the portal vein. CT during arterial portography is the gold standard to diagnosis of hepatic tumors. Percutaneous transhepatic portography is applied to perform interventional radiology such as percutaneous transhepatic portal embolization, percutaneous transhepatic obliteration of esophageal varices, or embolization of portosystemic shunts. In the case of portal vein obstruction, transileocolic vein portography is performed under laparotomy. Balloon-occluded retrograde transvenous venography is conducted to ascertain the development of the collateral veins before balloon-occluded retrograde transvenous obliteration. Hepatic venography is conducted under balloon occlusion of the hepatic vein, and wedged hepatic venography is utilized to investigate the portal pressure indirectly. Moreover, vascular anatomy of portal hypertension and pathological conditions such as esophageal varices, gastric varices, ectopic varices, or hepatic encephalopathy are described from the standpoint of hemodynamics.

Keywords Arterial portography · Superior mesenteric artery · Percutaneous transhepatic portography · Transileocolic vein portography · Hepatic venography · Balloon-occluded retrograde transvenous venography

S. Hirota (✉) · Y. Kako · K. Kobayashi
Department of Radiology, Hyogo College of Medicine, Konan Hospital IVR Center, Nishinomiya, Hyogo, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_15

15.1 Introduction

Modern angiographic equipment is equipped with C-arm cone-beam CT which is able to produce tomographic images and 3D angiographic images. In addition, so-called IR-CT, which is equipped with angiography equipment and gantry-type multi-detector-row CT, is installed in most of the large hospitals in Japan. These machines are able to produce tomographic images and 3D angiographic images. CT during arterial portography (CTAP) and CT during arteriography (CTA) are essential to make exact diagnosis for interventional radiology.

High-quality angiography can make diagnoses not only of hemodynamic abnormalities but also of the direction of flow to make accurate diagnosis of portal hemodynamics (Figs. 15.1 and 15.2). And portography via a catheter directly inserted into the portal vein is essential to performing interventional radiology such as percutaneous transhepatic portal embolization (PTPE), percutaneous transhepatic obliteration (PTO), or embolization of portosystemic shunts.

15.2 Method

15.2.1 Arterial Portography

15.2.1.1 Superior Mesenteric Artery: Portography Using Pharmacological Technique

First of all, pharmaceutical superior mesenteric artery (SMA) angiography using a vasodilator drug should be performed to achieve beautiful portography. First, 10 μg of a prostaglandin drug (Alprostadil, Tanabe Mitsubishi, Tokyo, Japan) is administered into the SMA, then SMA angiography is performed within 1 minute after injection of the drug. In the late phase of SMA angiography, dense portography image is obtained (Fig. 15.3), which makes it possible to diagnose the direction and the velocity of the portal flow. In the diagnosis of portal hypertension, information of the direction of flow and confirmation of the collateral portal veins are essential [3].

15.2.1.2 Celiac Arteriographic Portography

In the late phase of the celiac arteriography, we are able to observe portal branches such as the pancreaticoduodenal vein, gastric veins, splenic veins, portal trunk, and intrahepatic portal branches. In cases of splenic vein obstruction or stenosis, late phase of celiac arteriography shows anatomical details that facilitate understanding of the portal hemodynamics around the spleen. Left gastric arteriography using a vasodilator is performed to depict the left gastric veins, cardiac venous plexus, and esophageal varices.

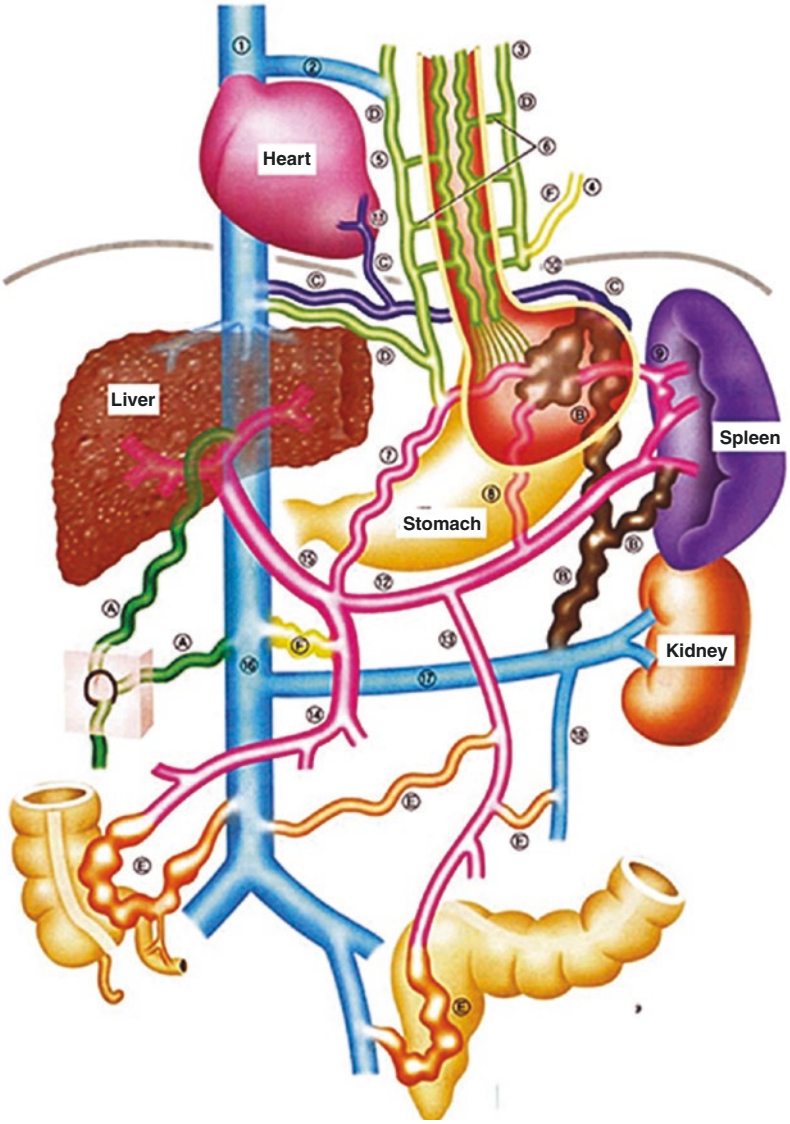


Fig. 15.1 Collateral pathways in portal hypertension (General Rules for Study of the Portal Hypertension The 3rd Edition edited by Japan Society for Portal Hypertension, 2013 [1]). ① Superior vena cava. ② Azygos vein. ③ Hemiazygos vein. ④ Pathway to the pulmonary vein. ⑤ Paraesophageal vein. ⑥ Perforating vein. ⑦ Left gastric vein. ⑧ Posterior gastric vein. ⑨ Short gastric vein. ⑩ Inferior phrenic vein. ⑪ Pericardial vein. ⑫ Splenic vein. ⑬ Inferior mesenteric vein. ⑭ Superior mesenteric vein. ⑮ Portal vein trunk. ⑯ Inferior vena cava. ⑰ Left renal vein. ⑱ Gonadal vein. A: Collateral pathway to the peritoneal wall. B: Collateral pathway to the renal vein. C: Collateral pathway to the phrenic vein. D: Collateral pathway to the azygos vein. E: Collateral pathway from the mesenteric vein. F: Pancreaticoduodenal vein shunt, portalpulmonary shunt etc.

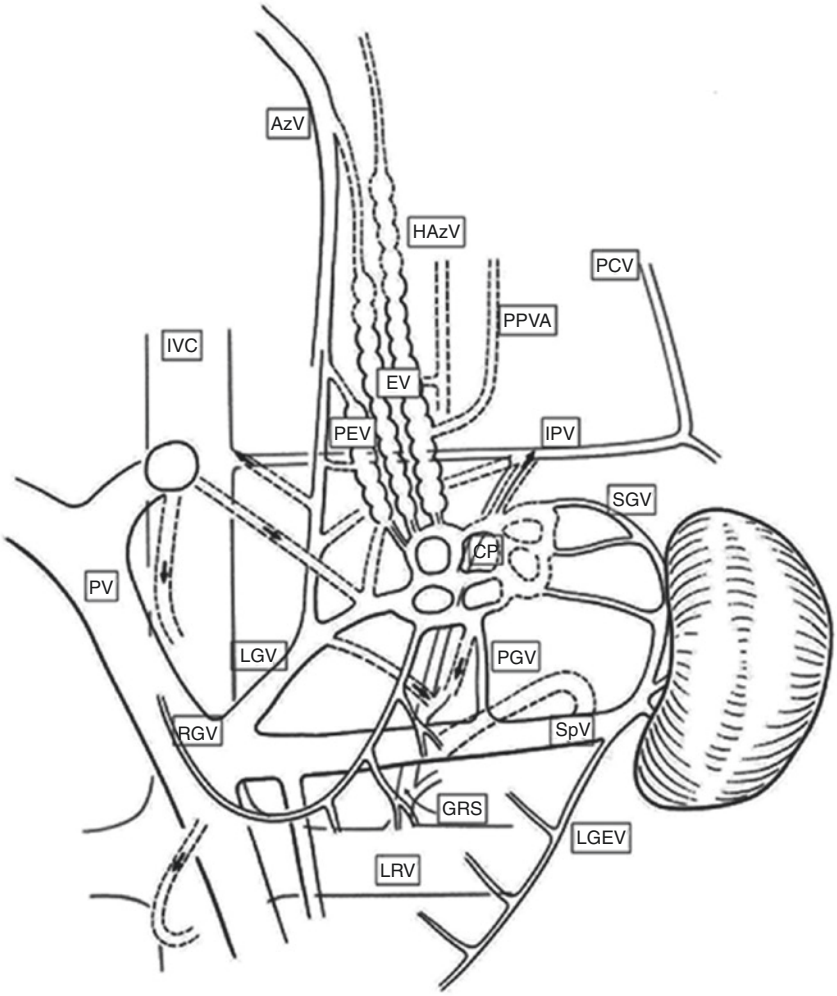


Fig. 15.2 Hemodynamics of esophagogastric varices (from the Atlas of portal hemodynamics edited by Takase Y, Igakushoin, 1999 [2]). *AzV* azygos vein, *Cp* cardiac venous plexus, *EV* esophageal varices, *GRS* gastrorenal shunt, *HAzv* hemiazygos vein, *IPV* inferior phrenic vein, *IVC* inferior vena cava, *LGV* left gastric vein, *LRV* left renal vein, *LGEV* left gastroepiploic vein, *PCV* pericardial vein, *PEV* paraesophageal vein, *PGV* posterior gastric vein, *PPVA* portopulmonary venous anastomosis, *PV* portal vein, *SGV* short gastric vein, *SpV* splenic vein

15.2.1.3 Splenic Arterial Portography

Splenic venography is conducted in order to perform selective splenic arteriography using vasodilator injection. In the late phase of splenic arteriography, the state of the splenic vein, short gastric vein, and collateral veins around the spleen is observed. In a case of left-sided portal hypertension due to splenic venous obstruction, splenic venography is important.

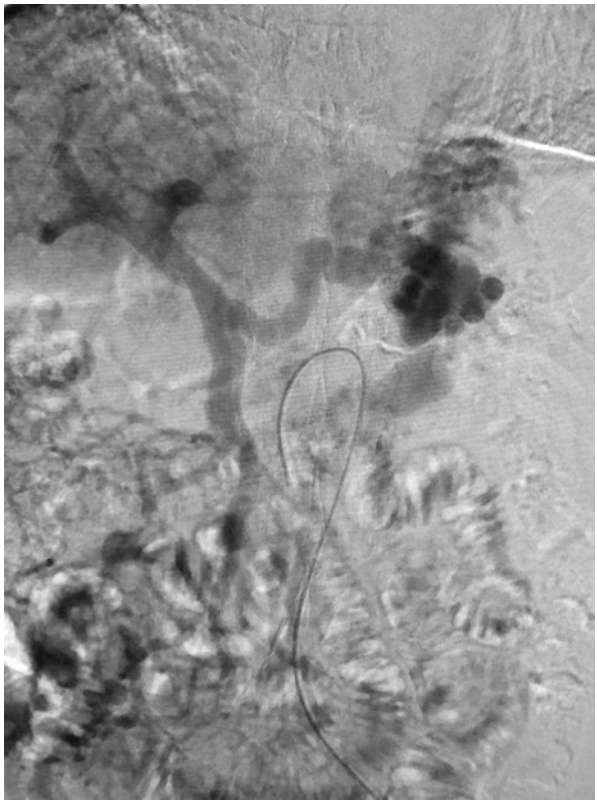


Fig. 15.3 SMA portography. Left gastric vein is markedly dilated and showed gastric varices and a gastrorenal shunt

15.2.2 Percutaneous Transhepatic Portography

To obtain direct portal venography, percutaneous transhepatic portography (PTP) is conducted using ultrasonographic-guided puncturing of the intrahepatic portal vein (Fig. 15.4a, b). In practice, PTP is performed to do portal interventions such as percutaneous transhepatic obliteration of varices (PTO) or percutaneous transhepatic portal embolization (PTPE).

15.2.3 Percutaneous Transsplenic Portography

Percutaneous transsplenic portography (PTSP) is not widely performed, but it is very useful as a means of obtaining portal venography in cases of portal trunk obstruction. After ultrasonographically guided puncturing of the intrasplenic vein, a thin catheter is introduced into the splenic vein. After the procedure, it is important to stop the bleeding securely from the catheter tract. Using n-butyl-cyanoacrylate (NBCA) as the embolic material is reported.

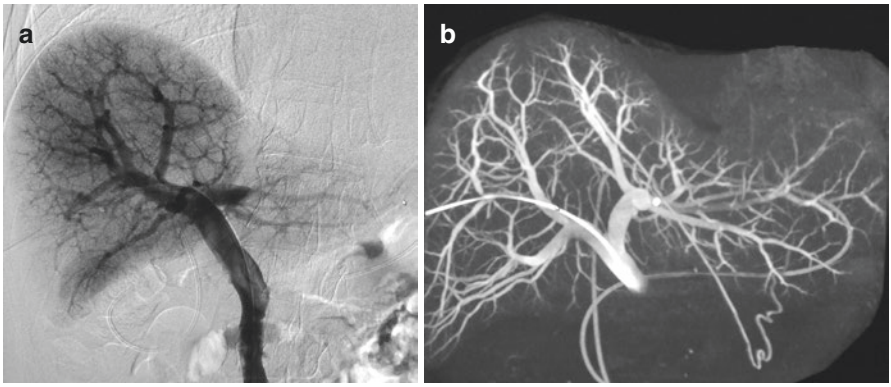


Fig. 15.4 (**a**) Percutaneous transhepatic portography (PTP). The catheter is located in the SMV; portography was taken. PTP showed portal trunk and intrahepatic portal branches. (**b**) Angio-3D view of the PTP was taken by C-arm cone-beam CT. The images can be rorated as desired

15.2.4 Balloon-Occluded Retrograde Venography

In order to obtain information on the hemodynamics of gastric varices and collateral veins, manually injected venography is performed under balloon occlusion of the gastrorenal shunt. There is a grading system of collateral veins based on the balloon-occluded retrograde venography (BRTV) (Fig. 15.5).

15.2.5 Hepatic Venography with Balloon Occlusion

A 5Fr balloon catheter is introduced into the right or left hepatic vein. Then under balloon occlusion of the hepatic vein, manually injected venography is performed. This is known to produce images with a weeping willow appearance in case of idiopathic portal hypertension. Moreover CO_2 angiography under balloon occlusion of the hepatic vein has the advantage of facilitating early portal vein depiction. This method is sometimes used to obtain an information of anatomical relationship between the hepatic vein and portal vein.

15.2.6 Transileocolic Vein Portography

In cases of portal trunk obstruction, the catheter is not able to be introduced transhepatically. Therefore, the guiding sheath is introduced from the ileocolic vein exposed under laparotomy. Then the catheter is inserted into the SMV, and direct portography is taken (Fig. 15.6). When postoperative anastomosing varices around the jejunostomy area cause jejunal bleeding, an IR procedure is conducted through the transileocolic vein route using this portography.

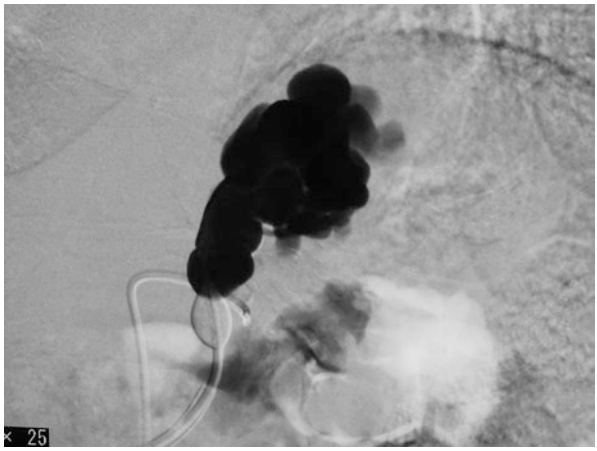


Fig. 15.5 A 65-year-old woman with huge gastric varices received B-RTO. Before B-RTO, BRTV (balloon-occluded retrograde transvenous venography) was performed. Huge gastric varices were shown

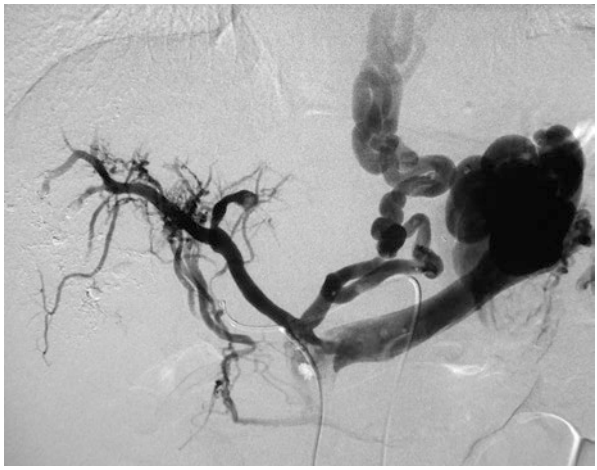


Fig. 15.6 Transileocolic vein portography. A patient with hemophilia is a relative contraindication of percutaneous transhepatic portography. Portography is conducted using the transileocolic vein approach. A dilated left gastric vein and gastric varices are shown clearly

15.3 Measurement of Portal Pressure

Measurement of portal pressure is important in estimating portal hypertension. Portal pressure was previously measured in cmH_2O, but nowadays mmHg is used because a pressure transducer is applied to estimate portal pressure. More than 15 cmH_2O is a criterion of portal hypertension, and varices of the portal system develop when the portal pressure increase to more than 20 cmH_2O. Conversion from cmH_2O to mmHg is as follows: 1 mmHg = 13.6 cmH_2O. However, to measure direct portal pressure, it is necessary to transhepatically puncture the intrahepatic portal vein and to indwell the catheter into the portal vein. Wedged hepatic venography (WHVP) is widely used to obtain information on portal pressure less invasively compared to transhepatically introduced catheter indwelling. WHVP is proportional to the postsinusoidal pressure

in patients with postsinusoidal block, e.g., liver cirrhosis. When veno-veno anastomosis exists, WHVP is not reflected in the postsinusoidal pressure. The pressure gradient from WHVP to free hepatic pressure is useful as an objective value.

15.4 Anatomy of the Portal Vein System

The main role of the portal system is carrying the nourishment absorbed in the gastrointestinal tract to the liver. Veins flowing into the portal vein include the splenic vein, pancreaticoduodenal vein, pancreatic vein, superior mesenteric vein, and inferior mesenteric vein (Fig. 15.1). In portal hypertension, a hepatopetal flow is generated and flows out through collateral veins to the systemic vein [4]. Along the course of developed collateral veins, varicose veins such as esophagogastric varices, ectopic varices, or portosystemic shunts are generated. The hemodynamics of esophageal varices has been described in detail by Japanese investigators. We have also reported on the hemodynamics of the gastric varices (see Chap. 38).

15.5 Pathological Condition of Portal Hemodynamics: Angiographic Findings

15.5.1 Arterioportal Shunt

Arterial-portal shunts are a phenomenon that shows up as early portal venous drainage on celiac arteriography. In liver cirrhosis, an AP shunt is often observed on the periphery of the liver, and it is also seen in the case of tumor thrombus with hepatocellular carcinoma, which is called a thread and streak sign [5]. Moreover, it is seen after aniatrogenically generated AP shunt, such as liver biopsy or percutaneous transhepatic biliary (PTCD). Once an AP shunt occurrs, it develops because of the high- to low-pressure steal phenomenon, and the portal pressure increases due to an increase in the portal venous inflow.

15.5.2 Esophageal Varices

In esophageal varices, the left gastric vein, posterior gastric vein, or short gastric vein flows out to the gastrocardiac venous plexus and pours out to the palisade vein and finally to the esophageal vein (Fig. 15.2). The increase in the flow generates esophageal varices and/or paraesophageal vein dilatation.

15.5.3 Gastric Varices

The supply routes for gastroesophageal varices are the left gastric vein and short/posterior gastric vein. The former is the major route for esophageal varices, and the latter is the major route for gastric varices. However, both veins flow into gastric varices very frequently as feeders. The blood that pours into the gastric varices on the posterior wall of the gastric fornix descends to flow from the inferior phrenic vein into the renal vein via the adrenal vein. This is called a gastrorenal shunt (GR shunt). In the ascending route, on the other hand, the blood from gastric varices flows into the inferior phrenic vein and pours into the inferior vena cava just above the left hepatic vein or into the left hepatic vein. Actually many retroperitoneal collateral veins come out on the BRTV in half of the cases after balloon occlusion of the GR shunt [6, 7].

The pericardiacophrenic vein runs along the edge of the left side of the heart and then pours into the left brachiocephalic vein. When the pericardiacophrenic vein is a major draining vein, a catheter can be advanced retrogradely through this orifice of the left brachiocephalic vein.

An anastomosis branches off to the pulmonary vein from the portal system in a small minority of cases, and balloon-occluded retrograde venography should be carefully scanned so as not to overlook it. If the sclerosant or embolus migrates into the left atrium, cerebral infarction may occur.

15.5.4 Ectopic Varices

Ectopic varices is a general term for spontaneously generated varices excluding gastroesophageal varices. The frequency of ectopic varices is 2–5% that of the gastrointestinal varices. The risk of bleeding from ectopic varices is four times higher than from esophageal varices. Once bleeding from ectopic varices occurs, the mortality rate is 40%. Among the ectopic varices, rectal varices are the most frequently generated varices at 45%, followed by duodenal varices at 33%, and small intestinal varices at 6.5%. After surgical intestinal anastomosis, jejunal varices rarely occur.

15.5.4.1 Duodenal Varices

Duodenal varices are fed from the superior or inferior pancreatico duodenal veins, and their flow drains out to the renal vein, renal capsular vein, or gonadal vein. Duodenal varices are generated in the descending part or the horizontal part.

15.5.4.2 Rectal Varices

Rectal varices are generated after the superior rectal vein refluxed from the inferior mesenteric vein drains into the middle and inferior rectal vein which drains to the internal iliac vein.

15.6 Portosystemic Shunts: Mesocaval Shunts

The mesenteric part of the superior mesenteric vein or inferior mesenteric vein dilates tortuously like a varicose vein and flows through the veins of Retzius vein and lumbar vein to the inferior vena cava (IVC) or internal iliac vein. The flow volume of this shunt is often large and causes hepatic encephalopathy.

15.7 Other Conditions of Portal Hypertension

15.7.1 Locoregional Portal Hypertension: Left-Sided Portal Hypertension

Left-sided portal hypertension is brought about by obstruction or severe stenosis of the splenic vein due to cancer, pancreatitis, or postoperative inflammation. Resultantly, collateral veins around the spleen such as the short gastric vein or the posterior gastric vein develop and form gastric varices.

15.7.2 Budd-Chiari Syndrome

Budd-Chiari syndrome means that a membranous obstruction of the hepatic part of the IVC and/or an obstruction of the hepatic vein brings about hepatic congestion causing liver fibrosis. Liver fibrosis leads to portal hypertension. In cases of membranous obstruction of the IVC, many collateral veins such as the ascending lumbar vein develop.

15.7.3 EHO: Extrahepatic Obstruction of the Portal Vein

Arterial portography shows an obstruction of portal vein trunk and a cavernous transformation of collateral veins.

15.7.4 Portal Thrombosis

The site of thrombus ranges from the periphery of the SMV to the portal trunk. On contrast-enhanced CT, thrombus can be precisely diagnosed. Arterial portography or splenic venography reveals a filling defect in the vein.

15.7.5 Summary

The role of angiography in patients with portal hypertension is described. Procedures such as arterial portography, transhepatic portography, transsplenic portography, balloon-occluded retrograde venography, hepatic venography, and transileocolic venography are important in order to obtain information on the pathological condition or pre-procedural information before interventional radiology.

References

1. Chikamori F. Angiography in clinical manual of portal hypertension edited by JSPH. Tokyo: Nankodo; 2015. p. 42–8.
2. Takase Y, et al. Atlas of portal vein hemodynamics for treatment of varices. Tokyo: Igaku Shoin; 1999.
3. Uflacker R. Atlas of vascular anatomy – an angiographic approach. Baltimore: Williams & Wilkins; 1997. p. 639–44.
4. Sharma M, Rameshbabu CS. Collateral pathways in portal hypertension. J Clin Exp Hepatol. 2012;2(4):338–52.
5. Cichoz-lach H, Celinski K, et al. Pathophysiology of portal hypertension. J Physiol Pharmacol. 2008;59(suppl2):231–8.
6. Watanabe K, et al. Portal hemodynamics in patients with esophageal and/or gastric varices using portal vein catheterization. Gastroenterology. 1988;95:434–40.
7. Witte CL, et al. Splenic circulatory dynamics in congestive splenomegaly. Gastroenterology. 1974;67:498–505.

Chapter 16
The Baveno IV Workshop: European Consensus Meeting on Portal Hypertension and Comparison with Japanese Guidelines

Naoya Murashima

Abstract In this chapter introducing the results of the discussions that took place in the consensus meeting on portal hypertension held on April 10–11, 2015 in Baveno, Italy, the Japanese guidelines published in 2016 are compared with the Baveno consensus on portal hypertension. The Baveno VI workshop honors the 25th anniversary of its organizer Prof. Roberto de Franchis.

Keywords Baveno · Consensus · Portal hypertension

16.1 Discussion on the Concept of Risk Stratification

At Baveno VI workshop [1–3], methods of screening for varices associated with portal hypertension were discussed. Almost all participants agreed that upper gastrointestinal endoscopy was the gold standard for diagnosing or suggesting portal hypertension. However, in Japan, to evaluate for hepatocellular carcinoma, computed tomography (CT) with contrast is usually performed, which can detect esophagogastric varices with portal venous phase imaging. When viral infection is eradicated or alcohol intake is controlled, the consensus on the optimal interval for endoscopy was 2 years at the Baveno workshop. Assessment of liver hardness with ultrasound (liver stiffness, LSS) was generally recognized as useful. Some, mostly French physicians, argued that transient elastography was the most useful technique for assessing the risk of variceal bleeding. A definitive diagnosis of cirrhosis can be made when LSS is greater than 20 kPa, whereas cirrhosis is unlikely when LSS is less than 10 kPa in the consensus discussion. For patients with LSS greater than 15 kPa and less than 20 kPa or greater than 20 kPa, careful observation is also necessary.

Moving away from the pathological concept of liver cirrhosis, a new concept of "compensated advanced chronic liver disease (cACLD)" was proposed. The value of cACLD should be verified prospectively [4, 5]. In Japan, measuring liver hardness

N. Murashima
Department of Gastroenterology, Mishuku Hospital, Meguro-ku, Tokyo, Japan
e-mail: murashima@mishuku.gr.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_16

with complicated procedures, such as measuring shear wave velocity during ultrasonography, has also been recognized as useful with a high evidence level. The superiority of such ultrasonographic techniques should be discussed in the future. The combination of CT or magnetic resonance imaging (MRI) examination with various serological markers is sometimes useful for evaluating the liver fibrosis.

The MELD score is still important. In addition, the risk of hyponatremia has been emphasized. In Japan, tolvaptan, a V2 receptor antagonist, is generally prescribed. It might correct hyponatremia and thus might improve the prognosis of liver cirrhosis. We hope to conduct research about the effectiveness of tolvaptan in Japan.

16.2 Problem with Statistical Methods

According to the lectures by Prof. D'Amico at the Baveno VI workshop, Kaplan–Meier analysis of the prognosis of liver cirrhosis is likely to overestimate the mortality rate because of the decreasing number of patients during observation. The Kaplan–Meier plot of the mortality rate will show the maximum value of mortality. Therefore, a Nelson–Aalen model or Aalen–Johansen model [6] should be used instead. It is necessary to master these statistical models announced in academic journals in Japan. Recently, with increases in the elderly population, comorbidities [7] will have a substantial influence on the cause of death and prognosis of patients with cirrhosis. Furthermore, "the risk" is clearly different from "the incidence," because the statistical methods are different.

16.3 Screening Tests for Portal Hypertension (Invasive and Noninvasive Methods)

Studies where LSS was examined using Fibroscan were common at the Baveno workshop; other methods were not presented. Detailed guidelines on liver elastography have already been published by the Japan Society of Ultrasound [8]. Spleen stiffness is also an important marker of portal hypertension. Advanced medical technologies to screen for portal hypertension such as multi-detector row CT (MDCT) or magnetic resonance (MR) elastography are useful in Japan, but they have not yet been announced to the world.

LSS greater than 15 kPa was proposed as the screening cutoff for ACLD. LSS less than 20 kPa and a platelet count over 150,000/μL suggest a low risk of variceal bleeding. Portal hypertension can be definitively diagnosed by hepatic venous pressure gradient (HVPG) measurement or endoscopy. Among these invasive methods, hepatic venous pressure measurement is still standard and important. The

interpretation of HVPG greater than 10 mmHg and prognosis has been reemphasized at the Baveno workshop. On the other hand, Prof. Boyer emphasized that screening endoscopy for portal hypertension should be avoided due to its high cost. The red color sign with esophagogastric varices is the most important finding in Japan for stratifying the risk of early bleeding; this sign is not well recognized in Europe. Japan's sophisticated endoscopic findings should be disseminated around the world.

Prof. Pinzani of the United Kingdom, Prof. Sherlock's successor, discarded the concept of cirrhosis that emerged from the studies of liver disease in the 1820s and supported ACLD. The concept of ACLD may be accepted in Japan, because esophageal varices sometimes develop before the pathological cirrhosis stage.

Many criteria for portal hypertension from the Baveno V workshop did not change at the VI workshop. Prognosis is evaluated with the 6-week survival rate. Treatment failure is still defined as requiring two units of blood (i.e., 400 ml) or an equivalent drop in hemoglobin within 24 h and overt rebleeding within 5 days. Clear criteria have not been decided in Japan.

16.4 Progress of Pharmacologic Treatments for Portal Hypertension

16.4.1 Impact of Antiviral Therapy and Antifibrotic Therapy on Portal Hypertension

At the Baveno VI workshop, Dr. Radosavljevic of the University of Vienna demonstrated that direct acting antiviral drugs for HCV reduced portal hypertension. Prof. Laleman from Belgium showed that portal pressure was reduced by weight loss and smoking cessation. Various drugs have been proposed as antifibrotic therapy. In summary, obeticholic acid, warfarin, enoxaparin [9], rifaximin, and simvastatin are promising, but sorafenib was not included. High-quality research on this issue is not found in Japan.

16.4.2 Rifaximin and Survival in Patients with Cirrhosis

In Europe, rifaximin, a poorly absorbed antibiotic that remains in the intestine, is commonly used. Rifaximin reduces levels of ammonia-producing bacteria and is useful in the treatment of hepatic encephalopathy. In addition, rifaximin has been shown to improve survival [10]. In contrast, lactulose, which is more commonly used, does not change the distribution of intestinal flora, so the effect for decreasing hyperammonemia is restricted.

16.4.3 Problem on Proton Pump Inhibitor

Prophylactic administration of proton pump inhibitors (PPIs) after endoscopic treatment for esophageal variceal bleeding is usually performed in Japan, but there are no studies with high-quality evidence. However, at the Baveno workshop, it was shown that PPIs were associated with worsening hepatic encephalopathy due to increased numbers of *Streptococcus* bacteria.

16.4.4 Beta-Blockade for Prevention of Decompensation and Rebleeding

Beta-blockade is a potent treatment for preventing decompensation of liver disease. Dr. Zipprich of Germany demonstrated that patients had improved HVPG on β-blockers; they achieved a certain extent of decompensation. In Japan, β-blockers are considered to be harmful in inducing heart block. In addition, the public health insurance system does not pay for β-blockers for prevention of decompensation. The major etiology of cirrhosis in Japan is hepatitis C. By contrast, cirrhosis is often the result of alcohol consumption in Europe. Regarding medical therapy for the primary prevention of bleeding, propranolol is the first choice of 55% of physicians in Europe, compared to 32% for carvedilol. In Japan, carvedilol is the first choice. Discontinuation of nonselective β-blockers (NSBBs) should be considered when systolic blood pressure becomes less than 90 mmHg, not when ascites develop. There is a consensus to stop NSBBs when kidney failure worsens. Prof. Groszmann emphasized that NSBBs are not effective in preventing rebleeding when HVPG is less than 10 mmHg.

16.5 Endoscopic Treatment for Prophylaxis of Variceal Bleeding

Regarding primary and secondary prophylactic treatment with endoscopy, endoscopic variceal ligation (EVL) is a consensus treatment, even for F1 varices in patients with Child C disease due to a high tendency to bleed. Endoscopic sclerotherapy (EIS) does not have validity in Baveno consensus [2, 3]. In Japanese guidelines [11], EIS is recommended rather than EVL for primary prevention of bleeding, based upon several randomized studies [12–14].

16.6 Treatment for Gastric Variceal Bleeding: Comparison of Baveno Consensus and Japanese Guidelines

There is a consensus on endoscopic tissue adhesive injection as a treatment for gastric variceal rupture in the Baveno consensus, just as in Japan. NSBB therapy is the dominant treatment, followed by tissue adhesive injection. In Europe, 4% of the

participants at the Baveno workshop considered balloon-occluded retrograde transvenous obliteration (B-RTO) as a secondary treatment, but it is widely practiced in Japan. At the Baveno workshop, transjugular intrahepatic portosystemic shunt (TIPS) followed by liver transplantation was also a major treatment [15], which is different from Japan. B-RTO is well recognized by European doctors but is not a common method to treat gastric varices. B-RTO revealed effective treatment results compared with TIPS in a case-controlled retrospective study [16] and a retrospective descriptive study [17]. Recently, a new report of a prospective trial was published by Japanese faculties [18]. In this study, the efficacy and safety of B-RTO were clarified for primary prevention of bleeding from isolated gastric varices. Nevertheless, it is necessary to conduct well-designed case-controlled and prospective studies in Japan in the future.

16.7 New Technique for Emergency Treatment for Esophageal Variceal Bleeding

In Europe, there is an impressive consensus for metal stent insertion in the distal esophagus instead of balloon tamponade to treat acute esophageal variceal bleeding [19]. At present, metal stents are not available in Japan.

16.8 Additional Medical Treatments After Hemostasis

Rifaximin reduced variceal rebleeding [20]. Enoxaparin did not reduce rebleeding but improved survival [7]. Branched amino acids may play a role in the prevention of decompensation in Japan as well as in Europe.

16.9 Consensus in the World

In Canada, a special report about the Baveno VI consensus workshop was published [21]. This report insists that the recommendations published by the workshop have all been thoroughly agreed upon by most physicians around the world. In the USA, B-RTO has become one of the major procedures to treat gastric varices. Meta-analysis revealed the safety and efficacy of B-RTO [22]. In Korea, B-RTO was proved to be an effective treatment for bleeding gastric varices [23].

16.10 Conclusion

Prophylactic EIS for esophageal varices and B-RTO for not only prophylactic but also elective treatments of gastric variceal bleeding are strongly recommended treatments in Japanese guidelines [11]. Further announcements from Japan will be an important task in the future.

References

1. Franchis R, editor. Portal hypertension VI: proceedings of the sixth Baveno consensus workshop; stratifying risk and individualizing care. Springer; 2016.
2. Tsochatzis EA, Bosch J, Burrough AK. Liver cirrhosis. Lancet. 2014;383(9930):1749–61.
3. Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension. J Hepatol. 2015;63:743–52.
4. Thabut D, Rudler M, Dib N, Carbonell N, Mathurin P, Saliba F, et al. Multicenter prospective validation of Baveno IV and Baveno II/III criteria in cirrhosis patients with variceal bleeding. Hepatology. 2015;61:1024–32.
5. Ahn SY, Park SY, Tak WY, Lee YR, Kang EJ, Park JG, et al. Prospective validation of Baveno V definitions and criteria for failure to control bleeding in portal hypertension. Hepatology. 2015;61:1033–40.
6. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis; the importance of multi-state models and competing analysis. Hepatology. 2015;62(1):292–302. https://doi.org/10.1002/hep.27598.
7. Jepsen P. Comorbidity in cirrhosis. World J Gastroenterol. 2014;20:7223–30.
8. Kudo M, Shiina T, Moriyasu F, Iijima H, Tateishi R, Yada N, et al. JSUM ultrasound elastography practice guidelines: liver. J Med Ultrason. 2013;40:325–57.
9. Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology. 2012;143:1253–60.
10. Vlachogiannakos J, Viazis N, Vasianopoulou P, Vafiadis I, Karamanolis DG, Ladas SD. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. J Gastroenterol Hepatol. 2013;28(3):450–5.
11. Fukui H, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51:629–50.
12. Iso Y, Kawanaka H, Tomikawa M. Repeated injection sclerotherapy is preferable to combined therapy with variceal ligation to avoid recurrence of esophageal varices; a prospective randomized trial. Hepato-Gastroenterology. 1997;44:467–71.
13. Gotoh Y, Iwakiri R, Sakata Y, Koyama T, Noda T, Matsunaga C, et al. Evaluation of endoscopic variceal ligation in prophylactic therapy for bleeding of oesophageal varices; a prospective, controlled trial compared with endoscopic injection sclerotherapy. J Gastroenterol Hepatol. 1999;14:241–4.
14. Akahoshi T, Tomikawa M, Tsutsumi N, Hashizume M, Maehara Y. Merits of prophylactic sclerotherapy for esophageal varices concomitant unresectable hepatocellular carcinoma; prospective randomized study. Dig Endosc. 2014;26:172–7.
15. Sauerbruch T, Mengel M, Dollinger M, et al. German Study Group for Prophylaxis of Variceal Rebleeding. Prevention of rebleeding from esophageal varices in patients with cirrhosis receiving small-diameter stents versus hemodynamically controlled medical therapy. Gastroenterology. 2015;149(3):528–31.
16. Sabri SS, Abi-Jaoudeh N, Swee W, Saad WE, Turba UC, Caldwell SH, et al. Short-term rebleeding rates for isolated gastric varices managed by transjugular intrahepatic portosystemic shunt versus balloon-occluded retrograde transvenous obliteration. J Vasc Interv Radiol. 2014;25:355–61.
17. Lee SJ, Kim SU, Kim MD, Kim YH, Kim GM, Park SI, et al. Comparison of treatment outcomes between balloon-occluded retrograde transvenous obliteration and transjugular intrahepatic portosystemic shunt for gastric variceal bleeding hemostasis. J Gastroenterol Hepatol. 2017;32(8):1487–94. https://doi.org/10.1111/jgh.13729.
18. Kobayakawa M, Kokubu S, Hirota S, Koizumi J, Nishida N, Yasumoto T, et al. Short-term safety and efficacy of balloon-occluded retrograde transvenous obliteration using ethanolamine oleate; results of a prospective, multicenter, single-arm trial. J Vasc Interv Radiol. 2017;28(8):1108–15. https://doi.org/10.1016/j.jvir.2017.03.041. pii: S1051-0443(17)30378-0

19. Hubmann R, Bodlaj G, Czompo M, Benko L, Pichler P, Al-Kathib S, et al. The use of self-expanding metal stents to treat acute esophageal variceal bleeding. Endoscopy. 2006;38:896–901.
20. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362(12):1071–81.
21. Cardenas A, Mendez-Bocanegra A. Report of the Baveno VI consensus workshop. Ann Hepatol. 2016;15:289–90.
22. Park JK, Saab S, Kee ST, Busutti RW, Kim HJ, Durazo F, et al. Balloon-occluded retrograde transvenous obliteration (BRTO) for treatment of gastric varices: review and meta-analysis. Dig Dis Sci. 2015;60:1543–53.
23. Choi YH, Yoon CJ, Park JH, Chung JW, Kwon JW, Choi GM. Balloon-occluded retrograde transvenous obliteration for gastric variceal bleeding: its feasibility compared with transjugular intrahepatic portosystemic shunt. Korean J Radiol. 2003;4:109–16.

Part III
Complications of Portal Hypertension: Gastrointestinal Varices

Chapter 17
Conservative Treatment: Pharmacological Therapy

Hisashi Hidaka

Abstract Current pharmacological therapy for the management of variceal hemorrhage consists of splanchnic vasoconstrictors (vasopressin and analogues, somatostatin and analogues, nonselective beta-blockers [NSBBs]), splanchnic vasodilators (nitrates and angiotensin receptor blockers), gastric acid-suppressive drugs, and prophylactic antibiotics. Several studies have shown that NSBBs are effective in decreasing portal venous pressure and the risk of variceal hemorrhage. However, approximately 15% of patients with risky varices have contraindications to the use of NSBBs. Furthermore, a meta-analysis showed that NSBBs did not significantly reduce the first variceal hemorrhage in patients with small varices. Further studies are warranted to determine the potential of drugs (besides NSBBs) as an alternative or adjunct to NSBBs.

Keywords Esophagogastric varices · Portal hypertension · Cirrhosis
Nonselective beta-blockers · Mortality

17.1 Introduction

Bleeding esophagogastric varices are the severest complications of portal hypertension and represent the leading cause of death in patients with cirrhosis. Esophageal varices develop in 50% of the patients with cirrhosis and bleed in approximately 15–20% [1].

In Japan, pharmacological therapy is not the first choice for the management of esophagogastric varices because surgery, endoscopic treatment, or interventional radiology has been developed and established as a standard of care. On the other hand, in the world, pharmacological therapy for the management of esophagogastric varices has been commonly performed. Current pharmacological therapy for the management of variceal hemorrhage consists of splanchnic vaso-

H. Hidaka
Department of Gastroenterology, Internal Medicine, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan
e-mail: hisashi7@kitasato-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_17

constrictors (vasopressin and analogues, somatostatin and analogues, nonselective beta-blockers [NSBBs]), splanchnic vasodilators (nitrates and angiotensin receptor blockers [ARBs]) [2, 3], gastric acid-suppressive drugs, and prophylactic antibiotics. Several studies have shown that NSBBs are effective in decreasing portal venous pressure and the risk of variceal hemorrhage [2, 3]. Such investigations have suggested that reducing the hepatic venous pressure gradient (HVPG) confers protection from the risk of bleeding and thereby increases survival [2, 3]. However, approximately 15% of patients with risky varices have contraindications to the use of NSBBs [2, 3]. Here, I review the pharmacological therapies, principally NSBBs, as a conservative treatment based on the newest information available.

17.2 Pharmacological Treatment Targets

The mechanism determining the onset of bleeding from esophagogastric varices has emphasized the role of increased portal venous pressure [3]. The level of patients with significant portal hypertension has been defined as clinically significant portal hypertension (CSPH), and the HVPG measurement is the gold standard method to diagnose CSPH, which is defined as HVPG ≥10 mmHg [4]. Recently, measurement of HVPG response to therapy added relevant information: a decrease in HVPG of at least 10% (the former definition was 20% [3, 5]) or ≤12 mmHg after treatment is clinically relevant in the setting of primary prophylaxis [4].

17.3 Pharmacological Treatment Drugs (Principally NSBBs)

17.3.1 Patients with no Varices or Small Varices

Groszmann et al. [6] evaluated the efficacy of NSBBs in preventing development of or first bleeding from gastroesophageal varices. They randomly assigned 213 patients with cirrhosis and portal hypertension (minimal HVPG of 6 mmHg) to receive Timolol, an NSBB (108 patients), or placebo (105 patients). During a median follow-up of 54.9 months, rates of the development of gastroesophageal varices or variceal hemorrhage did not differ significantly between the Timolol group and the placebo group (39% and 40%, respectively; $P = 0.89$) nor were there significant differences in the rates of ascites, encephalopathy, liver transplantation, or death. Serious adverse events were more common among patients in the Timolol group than among those in the placebo group (18% vs. 6%, $P = 0.006$) [6]. Furthermore, a meta-analysis showed that NSBBs did not significantly reduce the first variceal hemorrhage in patients with small varices [2]. Therefore, there is no indication, at this time, to use NSBBs to prevent the formation of varices or the first hemorrhage from small varices [3, 4].

17.3.2 Patients with Medium to Large Varices

Either NSBBs or endoscopic variceal ligation (EVL) is recommended for the prevention of a first variceal bleeding of medium to large varices [4]. Traditional NSBBs (e.g., propranolol, nadolol) are valid first-line treatments [4]. Carvedilol, a non-cardioselective vasodilating beta-blocker, is more effective in reducing portal pressure than is propranolol. Tripathi et al. [7] compared carvedilol and EVL for the prevention of the first variceal bleed in a randomized controlled multicenter trial. A total of 152 cirrhotic patients from five different centers with medium or larger esophageal varices were randomized to either receive carvedilol 12.5 mg once daily or undergo EVL every 2 weeks until eradication using a multibander device. Seventy-seven patients were randomized to receive carvedilol and 75 patients to undergo EVL. Baseline characteristics did not differ between the groups (alcoholic liver disease, 73%; median Child-Pugh score, 8; median age, 54 years; median follow-up, 20 months). The Carvedilol group had lower rates of the first variceal bleed (10% versus 23%, respectively; relative hazard 0.41; 95% confidence interval [CI] 0.19–0.96 [$P = 0.04$]), with no significant differences in overall mortality (35% versus 37%, respectively, $P = 0.71$), and bleeding-related mortality (3% versus 1%, respectively, $P = 0.26$). Six patients in the EVL group bled as a result of postbanding ulcers. Carvedilol may be more effective than traditional NSBBs in reducing HVPG [7, 8] but has not yet adequately been compared head-to-head to traditional NSBBs in clinical trials [4].

17.3.3 Combination of Pharmacological Therapy and Endoscopic Therapy

In a meta-analysis, Bañares et al. [9] assessed whether vasoactive drugs may improve the efficacy of endoscopic therapy (endoscopic injection sclerotherapy or EVL) in the control of acute variceal bleeding and thus increase survival rates. Combined treatment improved initial control of bleeding (relative risk [RR], 1.12; 95% CI, 1.02–1.23), and 5-day hemostasis (RR, 1.28; 95% CI, 1.18–1.39), with 8 and 5 patients requiring treatment, respectively. However, mortality was not significantly decreased by combined therapy (RR, 0.73; 95% CI, 0.45–1.18). Severe adverse events were similar in both groups. In conclusion, in patients with acute variceal bleeding, pharmacologic agents improve the efficacy of endoscopic therapy to achieve initial control of bleeding and 5-day hemostasis. On the other hand, in patients with recurrent variceal hemorrhage, the first-line therapy is the combination of NSBBs with adjuvant EVL [4].

17.3.4 Patients with Gastric Varices

Gastric variceal bleeding is severe and is associated with high mortality [10]. Mishra et al. [11] compared the efficacy of cyanoacrylate injection and beta-blockers as primary prophylaxes of gastric variceal bleeding. In that study, cirrhotics with large

gastroesophageal varices type 2 with eradicated esophageal varices or a large isolated gastric varices type 1, who had never bled from the varices, were randomized to receive cyanoacrylate injection (Group I, $n = 30$), beta-blockers (Group II, $n = 29$), or no treatment (Group III, $n = 30$). The primary end points were bleeding from a gastric varix or death. The actuarial probability of bleeding from gastric varices over a median follow-up of 26 months was 13% in Group I, 28% in Group II ($P = 0.039$), and 45% in Group III ($P = 0.003$). The actuarial probability of survival was higher in the cyanoacrylate compared to the no-treatment group (90% vs. 72%, respectively; $P = 0.048$) [11]. Although that study suggested that cyanoacrylate injections are more effective than NSBBs in preventing first bleeding in patients with large gastroesophageal varices or isolated gastric varices, further studies are warranted to evaluate the risk/benefit ratio of using cyanoacrylate in this setting [4, 10, 11].

17.4 Other Pharmacological Treatment Drugs (Besides NSBBs)

17.4.1 Isosorbide Mononitrate (ISMN)

Angelico et al. [12] investigated the long-term effects of isosorbide mononitrate (ISMN) vs. propranolol on first bleeding from esophageal varices, complications, and death in patients with cirrhosis. In this study, 108 patients comprising a previously published randomized trial comparing ISMN (20 mg tid) with propranolol were followed up for up to 7 years (range, 2–91 months). Fifty-seven patients received ISMN, and 61 patients received propranolol. Thirty episodes of first variceal bleeding occurred, 16 of which episodes were in the ISMN group. The actuarial probability of bleeding did not differ between the two groups. Of the 52 patients who died, 28 were in the ISMN group. The likelihood of death was greater among patients assigned to the ISMN group than among those assigned to the propranolol group but only in patients older than 50 years of age (72% vs. 48% at 6 years, respectively; $P = 0.006$).

17.4.2 Vasopressin

Vasopressin is the most potent splanchnic vasoconstrictor. It reduces blood flow to all splanchnic organs, thereby leading to a decrease in portal venous inflow and decreased portal venous pressure. The clinical usefulness of vasopressin is limited due to its multiple side effects, which are related to its potent vasoconstrictive properties, including cardiac and peripheral ischemia, arrhythmia, hypertension, and bowel ischemia [13]. Therefore, it can only be used continuously at the highest effective dose for a maximum of 24 h to minimize the development of side effects [13].

17.4.3 Terlipressin

Terlipressin is a synthetic analogue of vasopressin. It has a longer biological activity and significantly fewer side effects than does either ISMN or vasopressin. Therefore, it is effective in controlling acute variceal hemorrhage and has been associated with decreased mortality [2]; however, it has not been available for human therapy in Japan until recently.

17.4.4 Somatostatin and Its Analogues

Somatostatin causes splanchnic vasoconstriction at pharmacological doses. Although this effect is likely due to an inhibition of the release of vasodilatory peptides, mainly glucagon, studies have suggested that octreotide, an analogue of somatostatin, has a local vasoconstrictive effect [14]. The advantage of somatostatin and its analogues is that it is safe and can be used continuously for 5 days or longer [14].

17.4.5 Angiotensin Receptor Blocker (ARB)

Angiotensin II, the main peptide of the renin-angiotensin system, regulates cell growth, inflammation, and fibrosis and contributes to the progression of injury of various organs through angiotensin 1 (AT1) receptors [15]. Some studies indicated that the AT1 receptor antagonists: losartan [16], candesartan cilexetil (candesartan) [17], and olmesartan [18, 19] in selected cirrhotic patients were effective on portal pressure and liver fibrosis markers. Finally, Tandon et al. [20] reported that ARB reduced portal pressure in patients with only Child-Pugh A cirrhosis without adverse events. The efficacy and safety in this group may be secondary to a targeted effect on the local hepatic renin-angiotensin-aldosterone system (RAAS), as compared to decompensated patients who are at risk of hypotension and renal insufficiency due to activation of the systemic RAAS. Further studies are warranted to determine the potential of these drugs as an alternative or adjunct to NSBBs.

17.4.6 Gastric Acid-Suppressive Drugs (Proton Pump Inhibitors: PPIs)

Proton pump inhibitors (PPIs) are the most potent pharmacological agents for inhibition of gastric acid secretion [21]. Although PPIs will assuage the effect that gastric acid plays in post-EVL complications, there is one short-term study (10 days) that evaluated the role of PPIs after EVL [22]. In that study, Sheenan et al. reported that PPI treatment for only 9 days after EVL did not significantly reduce complications or

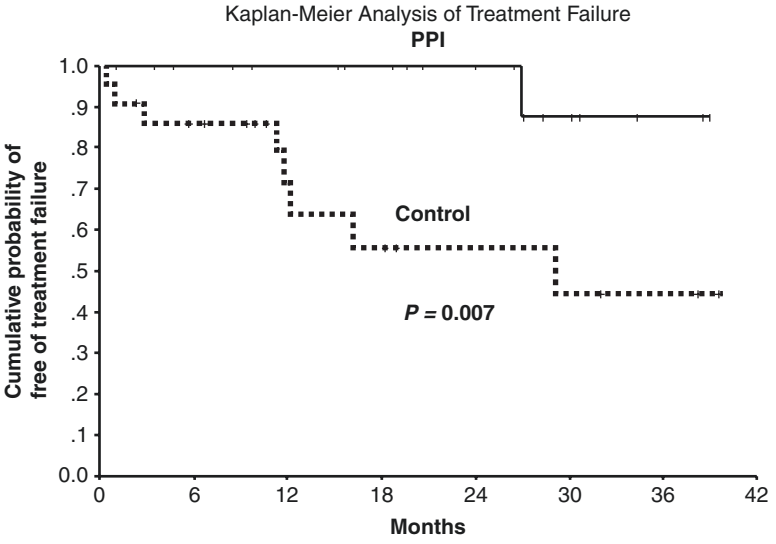


Fig. 17.1 The log-rank test showed a significant difference between the two groups ($P = 0.007$). This indicated a longer period without bleeding and no severe complications. The Cox proportional hazard regression model revealed that the PPI treatment reduced the risk of bleeding and severe complications by about ten times compared to that of the control treatment (hazard ratio, 0.098; 95% confidence interval [CI], 0.012–0.79; $P = 0.029$)

symptoms [22]. In another recent study, Hidaka et al. [23] reported that long-term administration of PPIs significantly reduced the risk of treatment failure after EVL (Fig. 17.1). However, that study may have been underpowered because the enrollment was not completed, e.g., only 21 patients receiving PPI therapy and 22 patients in the placebo group were included. Moreover, PPIs may modulate microbiota including spontaneous bacterial peritonitis (SBP) in patients with liver cirrhosis, which was one of the most serious complications in cirrhotic patients with ascites [24]. Intestinal permeability to bacteria generally increases in patients with cirrhosis [25], and bacterial translocations across the damaged gut developed SBP in these patients [26]. A large sample number and a long-term study are warranted to evaluate the risk/benefit ratio for the administration of PPIs in cirrhotic patients with esophagogastric varices.

17.5 Prophylactic Antibiotics

Variceal hemorrhage is associated with a high risk of bacterial infections (SBP and other infections) [27, 28]. Bernard et al. [27] investigated the incidence of bacterial infections in bleeding cirrhotic patients with variceal bleeding and the influence of

infections on the risk of rebleeding and death. In that study, 64 cirrhotic patients admitted for gastrointestinal bleeding who had not received antimicrobial chemotherapy in the previous 7 days were included. Blood, urine, and ascitic fluid cultures were systematically performed 1, 2, 4, and 7 days after admission. Within 7 days of admission, 42 bacterial infections were documented in 23 patients (36%). In patients with bacterial infections, the mean Child-Pugh score and mean number of blood units transfused were significantly higher than in those without bacterial infections, and early rebleeding was more frequent (43.5% vs. 9.8%, respectively; $P < 0.01$), and 4-week mortality was higher (47.8% vs. 14.6%, respectively; $P < 0.01$). Multivariate analysis only identified bacterial infections as predictive of early rebleeding ($P < 0.02$) and a high Child-Pugh score as predictive of death ($P < 0.001$).

Furthermore, Bernard et al. assessed the efficacy of antibiotic prophylaxis in the prevention of infections and its effect on the survival rate in cirrhotic patients with gastrointestinal bleeding [29]. Four end points were assessed: infection, bacteremia and/or spontaneous bacterial peritonitis (SBP), incidence of SBP, and death. Five trials including 534 patients, 264 treated with antibiotic prophylaxis for 4–10 days and 270 without treatment, were reviewed. Mean follow-up was 12 days. Antibiotic prophylaxis significantly increased the mean percentage of patients free of infection (32% mean improvement rate; 95% CI, 22–42; $P < 0.001$), bacteremia and/or SBP (19% mean improvement rate; 95% CI, 11–26; $P < 0.001$), and SBP (7% mean improvement rate; 95% CI, 2.1–12.6; $P = 0.006$). Antibiotic prophylaxis also significantly increased the mean survival rate (9.1% mean improvement rate; 95% CI, 2.9–15.3; $P = 0.004$), without significant heterogeneity. In cirrhotic patients with gastrointestinal bleeding, short-term antibiotic prophylaxis significantly increases the mean percentage of patients free of infection and the short-term survival rate.

References

1. North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med. 1988;319:983–9.
2. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. Semin Liver Dis. 1999;19:475–505.
3. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding—unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference. Hepatology. 2008;47:1764–72.
4. de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI consensus workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–52.
5. Turnes J, Garcia-Pagan JC, Abraldes JG, et al. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. Am J Gastroenterol. 2006;101:506–12.
6. Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med. 2005;353:2254–61.
7. Tripathi D, Ferguson JW, Kochar N, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology. 2009;50:825–33.

8. Reiberger T, Ulbrich G, Ferlitsch A, et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut. 2013;62:1634–41.
9. Bañares R, Albillos A, Rincón D, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. Hepatology. 2002;35:609–15.
10. Garcia-Pagán JC, Barrufet M, Cardenas A, et al. Management of gastric varices. Clin Gastroenterol Hepatol. 2014;12:919–28.
11. Mishra SR, Sharma BC, Kumar A, et al. Primary prophylaxis of gastric variceal bleeding comparing cyanoacrylate injection and beta-blockers: a randomized controlled trial. J Hepatol. 2011;54:1161–7.
12. Angelico M, Carli L, Piat C, et al. Effects of isosorbide-5-mononitrate compared with propranolol on first bleeding and long-term survival in cirrhosis. Gastroenterology. 1997;113:1632–9.
13. Bolognesi M, Balducci G, Garcia-Tsao G, et al. Complications in the medical treatment of portal hypertension. Portal Hypertension III. Proceedings of the Third Baveno International Consensus Workshop on Definitions, Methodology and Therapeutic Strategies. Oxford, UK: Blackwell Science; 2001. p. 180–203.
14. Lamberts SW, van der Lely AJ, de Herder WW, et al. Octreotide. N Engl J Med. 1996;334:246–54.
15. Yoshiji H, Kuriyama S, Yoshii J, et al. Angiotensin-II type 1 receptor interaction is a major regulator for liver fibrosis development in rats. Hepatology. 2001;34:745–50.
16. Schneider AW, Friedrich J, Klein CP. Effect of losartan, an angiotensin II receptor antagonist, on portal pressure in cirrhosis. Hepatology. 1999;29:334–9.
17. Debernardi-Venon W, Martini S, Biasi F, et al. AT1 receptor antagonist Candesartan in selected cirrhotic patients: effect on portal pressure and liver fibrosis markers. J Hepatol. 2007;46:1026–33.
18. Hidaka H, Kokubu S, Nakazawa T, et al. New angiotensin II type 1 receptor blocker olmesartan improves portal hypertension in patients with cirrhosis. Hepatol Res. 2007;37:1011–7.
19. Hidaka H, Nakazawa T, Shibuya A, et al. Effects of 1-year administration of olmesartan on portal pressure and TGF-beta1 in selected patients with cirrhosis: a randomized controlled trial. J Gastroenterol. 2011;46:1316–23.
20. Tandon P, Abraldes JG, Berzigotti A, et al. Renin-angiotensin-aldosterone inhibitors in the reduction of portal pressure: a systematic review and meta-analysis. J Hepatol. 2010;53:273–82.
21. Cotton PB, Williams CB. Practical gastrointestinal endoscopy. Cambridge, MA: Blackwell Science; 1996.
22. Shaheen NJ, Stuart E, Schmitz SM, et al. Pantoprazole reduces the size of postbanding ulcers after variceal band ligation: a randomized, controlled trial. Hepatology. 2005;41:588–94.
23. Hidaka H, Nakazawa T, Wang G, et al. Long-term administration of PPI reduces treatment failures after esophageal variceal band ligation: a randomized, controlled trial. J Gastroenterol. 2012;47:118–26.
24. Campbell MS, Obstein K, Reddy KR, et al. Association between proton pump inhibitor use and spontaneous bacterial peritonitis. Dig Dis Sci. 2008;53:394–8.
25. van Vlerken LG, Huisman EJ, van Hoek B, et al. Bacterial infections in cirrhosis: role of proton pump inhibitors and intestinal permeability. Eur J Clin Investig. 2012;42:760–7.
26. Guarner C, Runyon BA, Young S, et al. Intestinal bacterial overgrowth and bacterial translocation in cirrhotic rats with ascites. J Hepatol. 1997;26:1372–8.
27. Bernard B, Cadranel JF, Valla D, et al. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. Gastroenterology. 1995;108:1828–34.
28. Goulis J, Armonis A, Patch D, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. Hepatology. 1998;27:1207–12.
29. Bernard B, Grangé JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology. 1999;29:1655–61.

Chapter 18
Conservative Treatment: Balloon Tamponade

Masayuki Ohta, Masafumi Inomata, and Seigo Kitano

Abstract Balloon tamponade treatment for bleeding from esophagogastric varices with the Sengstaken-Blakemore (S-B) tube or Linton-Nachlas (L-N) tube was established in the 1950s. Now, after emergency endoscopy, the S-B tube is generally used for bleeding esophageal varices and the L-N tube is used for bleeding gastric varices. Because balloon tamponade with the S-B-tube is significantly inferior to endoscopic injection sclerotherapy (EIS) in the control of bleeding esophageal varices, the current indication for balloon tamponade is uncontrollable hemorrhage from esophagogastric varices caused by endoscopic treatments such as EIS. The contraindication is an anatomical abnormality in the esophagus such as esophageal stenosis, and careful use is required in patients with previous endoscopic treatments such as EIS. Balloon tamponade achieves primary hemostasis of variceal bleeding in 90% of the episodes and remains a clinically important modality even now.

Keywords Balloon tamponade · Bleeding esophagogastric varices · Sengstaken-Blakemore tube · Linton-Nachlas tube · Endoscopic injection sclerotherapy

18.1 Introduction

The concept of stopping hemorrhage at the site of ruptured esophageal varices by tamponade is not new; Westphal first reported a successful attempt at controlling esophageal hemorrhage by balloon tamponade in 1930 [1]. Afterward, many devices were developed, and Sengstaken et al. reported a new triple-lumen double-balloon tube, the so-called Sengstaken-Blakemore tube (S-B tube), in 1950 [2]. Linton reported the efficacy of balloon tamponade with a single-balloon tube in 1953 [3], and Nachlas also developed a new triple-lumen single-balloon tube, the so-called

M. Ohta (✉) · M. Inomata
Department of Gastroenterological and Pediatric Surgery,
Oita University Faculty of Medicine, Oita, Japan
e-mail: ohta@oita-u.ac.jp

S. Kitano
Oita University, Oita, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_18

Linton-Nachlas tube (L-N tube), in 1955 [4]. In Japan, Idezuki et al. developed a modified S-B tube that was transparent and had a lumen for observing the esophagus using a bronchoscope to check on hemostasis of the varices and the mucosal injury [5]. Although balloon tamponade by S-B tube is inferior to endoscopic injection sclerotherapy (EIS) in patients with bleeding from esophageal varices [6, 7], it still plays an important role in the clinical management of treatment for esophagogastric variceal bleeding [8]. Here, the technique and its results are demonstrated.

18.2 Current Devices and Indications/Contraindications of Balloon Tamponade Tubes

Presently, in Japan, three companies (Sumitomo Bakelite Co., Ltd., Tokyo; Top Co., Ltd., Tokyo; and Create Medic Co., Ltd., Yokohama) are selling balloon tamponade tubes for hemostasis of bleeding from esophagogastric varices. Figure 18.1 shows the current types of balloon tubes produced by Sumitomo Bakelite Co., Ltd. The S-B tube (TSB tube, A type) has four lumens that are combined into one lumen for draining the esophagus to prevent aspiration pneumonia and is known as a type of "Minnesota tube" [9] (Fig. 18.1a). The maximum capacity of the gastric balloon is 300 mL, and it is generally used for bleeding from esophageal varices. In contrast, the balloon tube of the L-N tube (TSB tube, single-balloon type) has three lumens and is similar to the original design (Fig. 18.1b). The maximum capacity of gastric balloon is 700 mL, and it is used for bleeding the gastric varices. Both types of tubes are made from silicon and incorporate X-ray markers.

The indication for balloon tamponade is uncontrollable hemorrhage from esophagogastric varices by endoscopic treatments such as EIS and endoscopic variceal ligation. Therefore, this treatment is only used as a temporary bridge to other strategies, and additional therapy should be performed after temporary hemostasis is

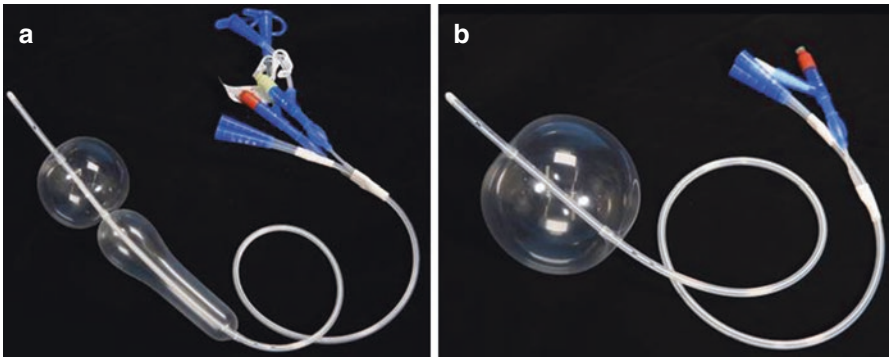


Fig. 18.1 Current models of balloon tamponade tubes (Sumitomo Bakelite Co., Ltd., Tokyo). (**a**) TSB tube, A type (S-B tube). (**b**) TSB tube, single-balloon type (L-N tube)

achieved. However, the contraindication of the balloon tamponade is an anatomical abnormality in the esophagus such as esophageal stenosis. Therefore, its use should be considered more carefully when a patient has undergone previous endoscopic treatments such as EIS.

18.3 Methods of Balloon Tube Placement

Before passage of the tube, the channels of the tube are tested for patency, and the balloons are checked for leaks. Because most of the patients have active bleeding from esophagogastric varices, tube passage has to be performed with the patient in the right lateral position if possible. The tube is lubricated with lidocaine jelly and passed through the nose into the stomach (up to more than 50 cm in length). Air is then injected into the stomach through the channel, and a stethoscope is used to detect the sound of air bubbles, which confirms that the tip of the tube is positioned within the stomach. However, it is more accurate to confirm the positions of the tip and the balloon by X-ray fluoroscopy. After confirmation of positioning, the gastric balloons are inflated with either 250–300 mL of air (A type, S-B tube) or 700 mL (single-balloon type, L-N tube). Although some of the literatures recommend that water be injected into the gastric balloon instead of air [10], we think that water should not be used instead of air to maintain the correct position of and prevent damage to the balloon. Then, the tube is slowly withdrawn until firm resistance is encountered at the esophagogastric junction (Fig. 18.2). After the tube is further retracted to apply pressure equal to 300–500 g of external traction, it is fixed with a sponge and tape. To prevent necrosis, the tube should not be retracted over the tip of the nose (Fig. 18.3). Afterward, the esophageal balloon of the S-B tube is inflated to a pressure of 30–40 mmHg as measured by manometry. The position of the tube and balloons is then checked using X-ray. Every hour, the esophageal and gastric contents are aspirated, and the traction of the gastric balloon is checked. To maintain the position of balloons and stop the bleeding from esophagogastric varices, it is of prime importance that the correct traction is applied. Gastric and esophageal balloons generally remain inflated for 12–48 h, but we recommend inflation for 12 h to prevent necrosis and/or injury of the esophagogastric junction. Therefore, the balloons should be deflated every 12 h.

Inadequate use of the S-B tube is illustrated in Fig. 18.4. A cirrhotic patient with bleeding esophageal varices was transferred from another hospital, and an S-B tube was placed. However, computed tomography revealed that balloons had slipped into the stomach because of inadequate traction and fixation of the balloon tube. Another cirrhotic patient with bleeding gastric varices who was also transferred had active bleeding from the varices in spite of S-B tube placement. When the balloon was deflated, 200 mL water was aspirated. This indicated that the balloon had not been maintained in an adequate position due to the weight of the water in the gastric balloon, and thus, the variceal bleeding could not be stopped.

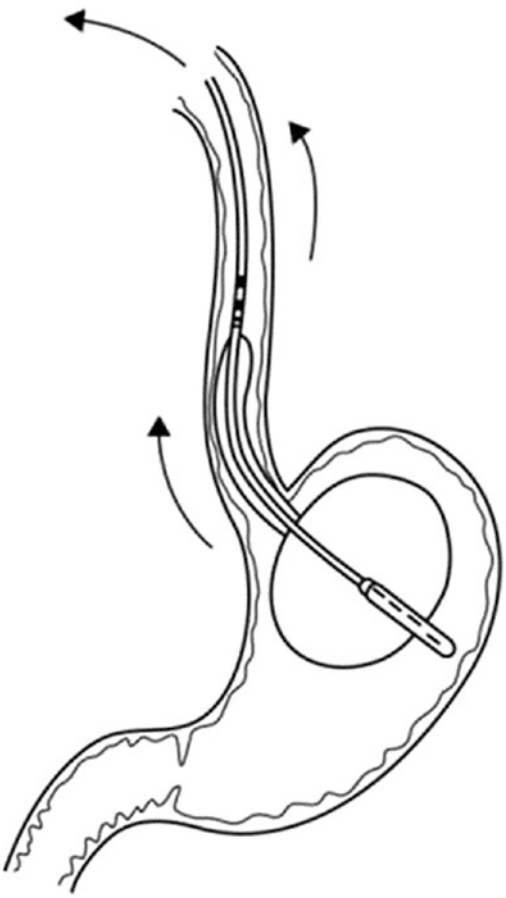


Fig. 18.2 Schematic of gentle withdrawal of the balloon tube after inflation of the gastric balloon with air

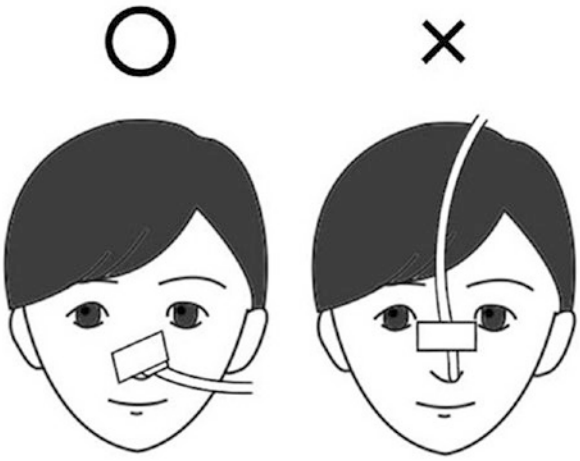


Fig. 18.3 Fixation method of the balloon tube at the nose. To prevent necrosis, the tube should not be retracted over the tip of the nose

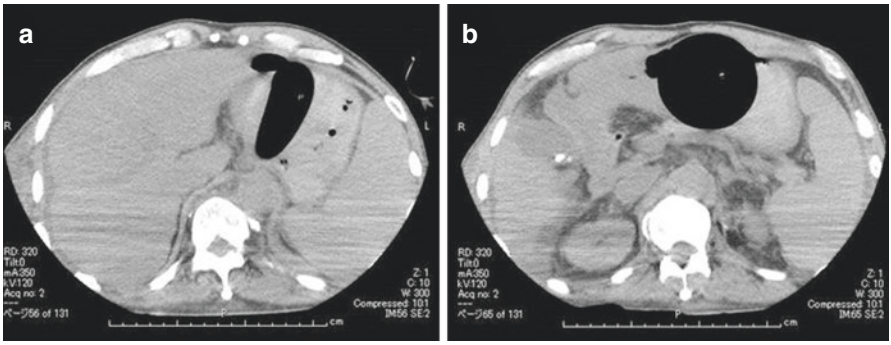


Fig. 18.4 Inadequate use of an S-B tube. Computed tomography revealed that the balloons had slipped into the stomach because of inadequate traction and fixation of the balloon tube. (**a**) The esophageal balloon is within the stomach. (**b**) The gastric balloon is far from esophagogastric junction

18.4 Results and Complications of Balloon Tamponade

Haddock et al. reported the results of the use of a modified S-B tube for acute variceal hemorrhage [10]. It stopped the bleeding in 98% of 126 episodes, but 36% of the patients with hemostasis experienced rebleeding. Complications included chest infection and esophageal tears. Panes et al. used an S-B tube in patients with bleeding esophageal varices and an L-N tube in those with gastric varices after endoscopy [11]. The S-B tube achieved primary hemostasis in 92% of 118 episodes and permanent hemostasis in 50%, and the L-N tube also achieved primary hemostasis in 88% of the 33 episodes and permanent hemostasis in 39%. Aspiration pneumonia occurred in 10% of the patients with the S-B tube and in 9% of those with the L-N tube. This complication appeared more frequently in patients with hepatic encephalopathy. Other complications included chest pain (17%), alae nasi necrosis (2%), and transient airway occlusion (1%).

Teres et al. performed a randomized controlled trial (RCT) to compare the S-B tube to the L-N tube in patients with active bleeding from esophagogastric varices [12]. Both tubes achieved primary hemostasis in over 90% of the patients with bleeding esophageal varices, but permanent hemostasis occurred more frequently with S-B tube (52%) than L-N tube (30%) use. The S-B tube failed in all three patients with bleeding gastric varices, but primary hemostasis was obtained with the L-N tube in 50% of such patients. With regard to complications, aspiration pneumonia occurred more frequently in patients with the S-B tube (29%) than in those with the L-N tube (10%). This study also reported that external traction on the S-B tube could cause adverse effects of complications and permanent hemostasis.

18.5 Comparison Between Balloon Tamponade and Other Treatments

Two RCTs have compared balloon tamponade to EIS in patients with bleeding esophageal varices [6, 7]. Paquet et al. demonstrated that the definite control of bleeding esophageal varices was significantly better in the EIS group (90%) than in the S-B tube group (55%) [6]. There was a significant difference in the number of the patients who died within 30 days between those treated with the S-B tube (27%) and those treated with EIS (10%). Moretó also found that primary hemostasis of bleeding esophageal varices was significantly better in the EIS group (100%) than in the S-B tube group (80%) [7]. At 7 days, only 56% of the patients with the S-B tube were free of hemorrhagic relapse, but 83% of the patients with EIS were relapse-free, and the difference was significant. Lo et al. performed another RCT to compare immediate EIS to EIS preceded by S-B tube use [13]. Rates of primary hemostasis and rebleeding were comparable in the two groups, but blood transfusion requirements and the incidence of complications were significantly lower in the immediate EIS group.

There have been two RCTs to compare balloon tamponade to drug therapies in patients with variceal bleeding [14, 15]. Teres et al. performed a RCT to compare vasopressin/nitroglycerin to balloon tamponade by S-B tube for bleeding esophageal varices and by L-N tube for bleeding gastric varices [14]. This trial found that hemostatic efficacy was significantly better in the balloon group (87%) than in the drug group (66%). No significant differences were recognized in rates of rebleeding, complications, and mortality. Avgerinos et al. compared three groups treated with somatostatin, balloon tamponade by S-B tube, or combined treatment [15]. Control of bleeding and mortality were comparable in the three groups, but the somatostatin alone group had significantly fewer complications than the other two groups.

18.6 Conclusion

Balloon tamponade achieved with S-B tube or L-N tube has been very effective in stopping hemorrhage from esophagogastric varices, but it is inferior to endoscopic treatments such as EIS and causes frequent complications such as aspiration pneumonia. Therefore, this treatment should be used only in patients with uncontrollable bleeding from esophagogastric varices as a temporary means of treatment.

References

1. Whestpal K. Uber eine Kompressionsbehandlung der Blutungen aus Oesophagusvarizen. Deutsche Med Wchnschr. 1930;56:1135–6.
2. Sengstaken RW, Blakemore AH. Balloon tamponage for the control of hemorrhage from esophageal varices. Ann Surg. 1950;131:781–9.
3. Linton RR. The emergency and definitive treatment of bleeding esophageal varices. Gastroenterology. 1953;24:1–9.
4. Nachlas MM. A new triple-lumen tube for the diagnosis and treatment of upper gastrointestinal hemorrhage. N Engl J Med. 1955;252:720–1.
5. Idezuki Y, Hagiwara M, Watanabe H. Endoscopic balloon tamponade for emergency control of bleeding esophageal varices using a new transparent tamponade tube. Trans Am Soc Artif Intern Organs. 1977;23:646–51.
6. Paquet KJ, Feussner H. Endoscopic sclerosis and esophageal balloon tamponade in acute hemorrhage from esophagogastric varices: a prospective controlled randomized trial. Hepatology. 1985;5:580–3.
7. Moretó M, Zaballa M, Bernal A, Ibáñez S, Ojembarrena E, Rodriguez A. A randomized trial of tamponade or sclerotherapy as immediate treatment for bleeding esophageal varices. Surg Gynecol Obstet. 1988;167:331–4.
8. Yoshida H, Mamada Y, Taniai N, Yoshioka M, Hirakata A, Kawano Y, et al. Treatment modalities for bleeding esophagogastric varices. J Nippon Med Sch. 2012;79:19–30.
9. Edlich RF, Lande AJ, Goodale RL, Wanggensteen OH. Prevention of aspiration pneumonia by continuous esophageal aspiration during oesophgogastric tamponade and gastric cooling. Surgery. 1968;64:405–8.
10. Haddock G, Garden OJ, McKee RF, Anderson JR, Carter DC. Esophageal tamponade in the management of acute variceal hemorrhage. Dig Dis Sci. 1989;34:913–8.
11. Panes J, Teres J, Bosch J, Rodes J. Efficacy of balloon tamponade in treatment of bleeding gastric and esophageal varices. Results in 151 consecutive episodes. Dig Dis Sci. 1988;33:454–9.
12. Teres J, Cecilia A, Bordas JM, Rimola A, Bru C, Rodes J. Esophageal tamponade for bleeding varices. Controlled trial between the Sengstaken-Blakemore tube and the Linton-Nachlas tube. Gastroenterology. 1978;75:566–9.
13. Lo GH, Lai KH, Ng WWN, Tam TN, Lee SD, Tsai YT, et al. Injection sclerotherapy preceded by esophageal tamponade versus immediate sclerotherapy in arresting active variceal bleeding: a prospective randomized trial. Gastrointest Endosc. 1992;38:421–4.
14. Teres J, Planas R, Panes J, Salmeron JM, Mas A, Bosch J, et al. Vasopressin/nitroglycerin infusion vs. esophageal tamponade in the treatment of acute variceal bleeding: a randomized controlled trial. Hepatology. 1990;11:964–8.
15. Avgerinos A, Klonis C, Rekoumis G, Gouma P, Papadimitriou N, Raptis S. A prospective randomized trial comparing somatostatin, balloon tamponade and the combination of both methods in the management of acute variceal haemorrhage. J Hepatol. 1991;13:78–83.

Chapter 19
Conservative Treatment: Nutritional Treatment

Ryujin Endo and Yasuhiro Takikawa

Abstract In liver cirrhosis, the nutritional elements and the energy metabolism are disturbed, resulting in the status of protein-energy malnutrition (PEM). PEM is common in patients with liver cirrhosis and is also a significant predictor of complications and survival in these patients. On the other hand, the bleeding from esophagogastric varices is still a major and severe complication affecting the prognosis of liver cirrhosis. Although endoscopic therapy and interventional radiology therapy have been widely performed as treatments for portal hypertension, the patients often require dietary restriction after these treatments, resulting in the aggravation of PEM. It has recently become evident that late evening snack improved the status of energy malnutrition and long-term oral administration of branched-chain amino acids (BCAA) supplements decreases the progression of hepatic failure and improves the event-free survival and quality of life, as well as the serum albumin concentration, in patients with decompensated liver cirrhosis. In addition, diet with BCAA-enriched nutrient supplementation may prevent the aggravation of nutritional status in patients with liver cirrhosis during the treatment of portal hypertension.

Keywords Protein-energy malnutrition (PEM) · Hepatic encephalopathy · Branched-chain amino acids (BCAA) · Late evening snack (LES) · Liver cirrhosis

R. Endo (✉)
Division of Medical Fundamentals for Nursing, Iwate Medical University, Shiwa, Iwate, Japan
e-mail: ryuendo@iwate-med.ac.jp

Y. Takikawa
Division of Hepatology, Department of Internal Medicine, Iwate Medical University, Morioka, Iwate, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_19

19.1 Introduction

Endoscopic therapy and interventional radiology (IVR) therapy have been widely performed as treatments for portal hypertension, enabling less invasive treatment. However, patiens often develop hepatic encephalopathy and exacerbation of ascites due to the deterioration of nutritional status and liver dysfunction during the perioperative period. Further, esophagogastric varices combined with liver cirrhosis often recur, with the determination regarding whether or not to continue therapy depending on the hepatic reserve. Therefore, it is extremely important to conduct proper nutrition management, taking into consideration the clinical condition based on liver dysfunction, along with the treatment for varices.

In this article, we outline the features of the nutritional metabolism of liver cirrhosis and explain actual nutritional therapy during treatment for portal hypertension.

19.2 Significance of Nutritional Therapy for Liver Cirrhosis

The occurrence of protein-energy malnutrition (PEM) among patients with cirrhosis is high, and patients with remarkable malnutrition are associated with a high occurrence of complications and mortality [1, 2].

Recently, enteral nutrition against liver cirrhosis has been shown to improve liver function and nutritional status, inhibit the development of complications, and improve the survival rate [2]. Furthermore, the oral administration of branched-chain amino acid (BCAA) preparations for the purpose of correcting PEM prolongs the patient's survival duration [3], indicating the medical validity of nutritional therapy.

19.3 Characteristics of Nutritional Metabolic Disorders Related to Liver Cirrhosis

19.3.1 Energy Consumption

In patients with cirrhosis, the resting energy expenditure (REE) is exacerbated [4]. The exacerbation of REE increases with the progress of severity [5], particularly markedly in the event of ascites, spontaneous bacterial peritonitis (SBP), liver cancer, and circulatory dynamic instability accompanying the ruptured esophagus and gastric varices [6, 7]. As a mechanism by which energy consumption becomes exacerbated, it is considered that the respiratory and circulatory systems are in a hyperdynamic state and both hormones and cytokines are involved in the hypermetabolism.

19.3.2 Substrate Utilization

In liver cirrhosis, despite the exacerbation of REE, the glycogen storage capacity is insufficient, and the skeletal muscle mass decreases due to gluconeogenesis from amino acids by degrading the muscle protein, which is in a state of negative nitrogen equilibrium. Moreover, the substrate utilization after overnight fasting is said to be equivalent to the 3-day fasting state of a healthy person, having the characteristics of a significantly reduced respiratory quotient and higher use of endogenous fat than in healthy people [4, 5]. Substrate oxidation rates are known to reflect the severity of the liver dysfunction (Fig. 19.1), with patients having low values of respiratory quotients below 0.85 known to have poor prognoses [8]. A reduction in the amount of glycogen stored in the liver and impaired glucose tolerance (reduction in insulin resistance and glucose utilization) are considered to be factors involved in the change in substrate utilization.

19.3.3 Metabolic Disorders of Protein/Amino Acids

Protein metabolic disorders related to liver cirrhosis occur as hypoalbuminemia, and patients with serum albumin levels less than 3.5 g/dL have a significantly lower survival rate [9]. In addition, BCAA in plasma decreases because the use of BCAA as an energy substrate for ammoniation in the skeletal muscles and gluconeogenesis is enhanced, while aromatic amino acids (AAA) and methionine which are metabolized in the liver increase as the severity of cirrhosis worsens. These metabolic disorders of amino acids are characterized by a decrease in the Fischer ratio

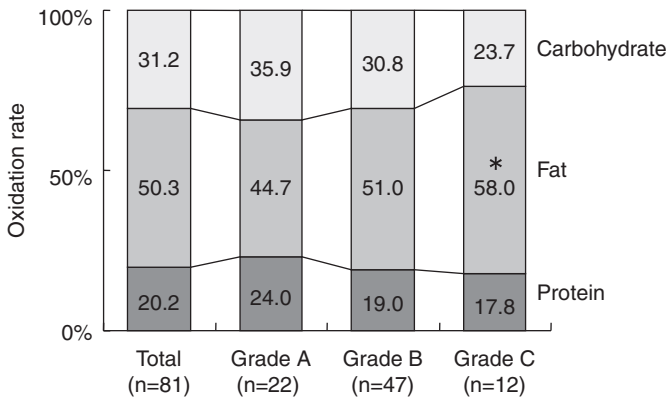


Fig. 19.1 Substrate oxidation rates of glucose, fat, and protein using indirect calorimetry in patients with liver cirrhosis. Seventy cirrhotic patients who were admitted to Iwate Medical University Hospital were investigated. Energy metabolism was measured using indirect calorimetry (Deltatrac-II Metabolic Monitor, Datax Division Inst. Corp., Helsinki, Finland) in the morning after overnight fasting. Each value is shown as the mean. *$P < 0.05$ (compared to grade A). n, number of patients with liver cirrhosis

(BCAA/tyrosine + phenylalanine) and BTR (BCAA/tyrosine ratio). A decrease in BCAA promotes the brain migration of AAA, resulting in an increase in false neurotransmitters, which is a cause of hepatic encephalopathy.

19.3.4 Characteristics of Complicated Hepatic Encephalopathy

Hepatic encephalopathy is a neuropsychiatric symptom centered on consciousness disorders caused by severe hepatic disorder, ranging widely from mild symptoms such as decreased orientation and abnormal behavior to a deep coma with no response whatsoever even if a stimulus is applied. Encephalopathy seen in cirrhosis is classified into a type with a strong factor of portal systemic shunt (chronic recurrent type) and another type with a strong factor of hepatocellular disorder (end-stage type). Determination of the severity of the liver dysfunction is important because the treatment effect and prognosis depend on it. As toxic substances such as ammonia generated in the intestinal tract are often derived from dietary proteins. Cirrhotic patients with portal systemic shunt are in a clinical condition which easily causes hepatic encephalopathy due to an excessive intake of protein (protein intolerance).

19.4 Nutritional Therapy

19.4.1 Basic Policy

We examined the following items to make a nutritional therapy plan, including the subjective global assessment (SGA) and biochemical parameters of nutritional status, clinical stage (compensatory or non-compensatory), presence or absence of hepatic encephalopathy, degree of coma, and the occurrence of complicated diabetes mellitus (Table 19.1) [10].

As the clinical condition of patients with a high level of ascites retention and edemas changes constantly with treatment, it is important to conduct nutritional assessments over time. If esophageal varices are present, the nutritional administration routes need to be flexible in accordance with individual cases [2, 11].

19.4.2 Measures for Energy Metabolism Abnormality

In order to compensate for the energy supply from dinner to the next morning for cirrhosis patients in a state similar to hunger at night, we divided approximately 200 kcal from the target total calories and fed it as a snack before going to bed, which is a method called late evening snack (LES) that has been recommended in clinical practice guidelines in Japan and Western countries [1, 2, 10, 12]. According

Table 19.1 Recommendations for nutritional management of liver cirrhosis

I. Assessment before nutrition and diet therapy
1. Evaluate clinical stage (compensated or decompensated liver cirrhosis) and the severity of liver damage (i.e., Child-Pugh classification) as well as presence of portal systemic shunt
2. Perform subjective global assessment (SGA) and anthropometry
3. Evaluate impaired glucose tolerance, insulin resistance, and postprandial hyperglycemia
4. Evaluate oxidative stress conditions
5. Examine dietary intake using a questionnaire
6. Perform indirect calorimetry and trace element measurement
II. Nutrition and diet therapy
1. Energy requirements 25–35 kcal/kg (ideal body weight)/day, based on standards for dietary intake (2010 edition, Recommended Dietary Allowance According to Intensity of Daily Activity) If any abnormalities are seen in glucose tolerance, intake should be 25 kcal/kg (ideal body weight)/day
2. Required protein intake If there is no protein intolerance: 1.0–1.5 g/kg/day (including oral BCAA granules) If there is protein intolerance: 0.5–0.7 g/kg/day + BCAA-enriched enteral nutrient mixture
3. Required fat intake: lipid energy ratio 20–25%
4. Sodium chloride: ≤6 g/day, and <5 g/day if there are ascites and/or edema
5. Iron: ≤7 mg/day if serum ferritin levels are above the upper limit of the reference interval
6. Others: zinc supplementation, adequate intake of vitamins and dietary fiber (vegetables, fruits, potatoes)
7. Late evening snack (LES) as a divided meal (4 times per day) (amounts to 200 kcal)

BCAA branched-chain amino acid (based on Suzuki et al. [10])

to the Japanese Society of Gastroenterology, cases of nonprotein respiratory quotient <0.85 are indicated for LES [12].

Ordinary food or general enteral nutrients may be used. However, by using BCAA-enriched nutrient mixture (e.g., Aminoleban® EN, 210 kcal; Hepan ED®, 310 kcal), the serum albumin concentration increases, and the oxidation rates for nutrients (carbohydrate, fat) after overnight fasting is improved. Therefore, maintenance of nitrogen balance, improvement of energy metabolic disorders, and impaired glucose tolerance can be expected through the long-term oral supplementation with a BCAA-enriched mixture use in LES [10, 12–14]. In addition, when LES is performed, it is important that the total daily calorie intake does not increase because LES leads to potential obesity and deterioration of impaired glucose tolerance by simply adding it to the previous meals.

19.4.3 Measures for Metabolic Disorders of Protein/Amino Acids

Dietary therapy centered on BCAA substitution therapy occupies the central position of nutritional treatment aimed at the correction of amino acid imbalance and negative nitrogen equilibrium along with the synthesis promoting effect of albumin,

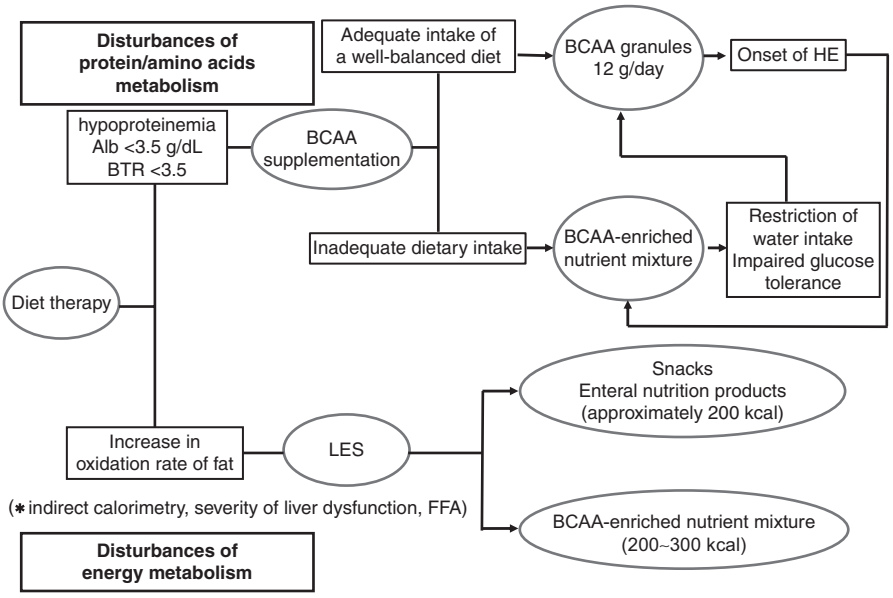


Fig. 19.2 Nutritional treatment for PEM in patients with liver cirrhosis. *PEM* protein-energy malnutrition, *BCAA* branched-chain amino acid (valine + leucine + isoleucine), *BTR* BCAA/tyrosine ratio, *LES* late evening snack, *HE* encephalopathy, *FFA* free fatty acid. Asterisk—indirect calorimeters are available, measurement of resting energy expenditure, nonprotein respiratory quotient (npRQ), and oxidation rates for various nutrients (carbohydrate, fat, protein) after overnight fasting is useful in evaluating protein-energy malnutrition. Serum free fatty acid levels are useful indexes for npRQ during routine care

which is also recommended in the clinical practice guidelines in Japan and Western countries [2, 10, 12].

Oral BCAA preparations include BCAA granules (Livact® Granules) and enteral nutrients for liver failure (e.g., Aminoleban® EN, Hepan ED®), which are selected depending on the severity of energy malnutrition and the presence or absence of hepatic encephalopathy (Fig. 19.2). The former is indicated for patients with hypoalbuminemia (3.5 g/dL or less) despite adequate amounts of a well-balanced diet intake, while the latter is indicated for those after awakening from hepatic encephalopathy or having a history thereof, involving chronic liver failure accompanied by protein intolerance. Even with a history of encephalopathy, the granule preparation can be administered as long as a balanced diet is sufficiently ingested and ammonia is under control. On the other hand, even with no history of encephalopathy, if dietary intake is insufficient, it is also effective to select enteral nutrients from the viewpoint of improving nutritional metabolism [15]. Therefore, in choosing an oral BCAA preparation, it is important to sufficiently grasp the decrease in intake amount and the presence or absence of bias in nutritional balance via a dietary survey.

19.5 Nutrition Management in the Treatment of Esophagogastric Varices

19.5.1 Nutrition Management during Emergency Hemostasis

19.5.1.1 Nutrition Administration Routes and Basic Infusion

In the case of bleeding of the esophagogastric varices, because liver failure advances due to a decrease in the circulating plasma volume, we strive to stabilize the circulatory dynamics. As a basic infusion, an extracellular solution replenisher, such as bicarbonate Ringer's solution (e.g., Bicarbon®, Bikanate®) or glucose-added acetate Ringer's solution (e.g., Veen-D®), is administered from the peripheral vein, switching to saccharification maintenance infusion (no amino acid) centering on glucose after hemostasis to control the general condition. For patients whose circulation dynamics are stable and oral intake is expected to be possible at a relatively early stage (within 1–2 weeks), peripheral parenteral nutrition (PPN) is often selected because they have some degree of calorie deficiency and should start oral intake as soon as possible. The indication for total parenteral nutrition (TPN) is limited to cases such as cardiorenal disease requiring water restriction and those requiring long-term fasting, etc.

19.5.1.2 Strategies for Treatment of Hepatic Encephalopathy

In the case of gastrointestinal bleeding, blood stored in the intestinal tract is decomposed, with ammonia produced by bacterial urease, consequently often resulting in hyperammonemia. The basis of treatment is the removal of toxic substances centering on ammonia and correction of metabolic abnormalities including amino acids, with drug therapy and infusion carried out along with the elimination of incentives and systemic management. Depending on the clinical condition of the patient, in the event of overt encephalopathy (grade II or higher) or in order to improve hyperammonemia, the enema administration of synthetic disaccharides (lactulose syrup) (not covered by insurance) is carried out, or BCAA enriched amino acid solution (e.g. Aminoleban®, Morihepamin®) is administered [11, 13].

BCAA-enriched amino acid solution should be intravenously infused usually within the range of 200–500 mL/day, taking into consideration the nitrogen treatment capacity of the patient. Fasting is continued in the far-advanced stage of comas in which oral intake is difficult, monitoring the extent of conscious awareness and blood ammonia values with the infusion basically containing BCAA and glucose. By using a BCAA infusion, the awakening effect can be obtained at an early stage chronic recurrent type cases, while in end-stage type cases in which the hepatic reserve capacity has declined, hyperammonemia and encephalopathy may be aggravated. Therefore, it is necessary to avoid excessive administration. Further, since it

may cause hypoglycemia after administration, it is also important to monitor blood sugar levels and use glucose solutions in combination (or coinjection).

When patients recover from encephalopathy and oral intake becomes possible, we switch to one to two packs/day of enteral nutrients for the patients with liver failure as soon as possible, gradually adding a low-protein diet [2]. However, it is noteworthy that unnecessary protein restriction tends to make nitrogen equilibrium negative, further promoting PEM. Nutritional therapy should be started with the total energy within the range of 25–35 kcal/kg/day, concurrently using a low-protein diet (0.5–0.7 g/kg/day) and enteral nutrition for patients with liver failure (e.g., one or two packs/day of Aminoleban EN® or Hepan ED®), so that the body constituents can be maintained [10].

19.5.2 Nutritional Management During Preventive/Palliative Treatment

During preventive and palliative endoscopic therapy, we tried to improve the nutritional status, control ascites and hepatic encephalopathy, and correct blood glucose and electrolytes as much as possible prior to surgery.

In the perioperative period of treatment, patients are often forced to fast, which is a concern that PEM may be further exacerbated. Therefore, we have patients who start oral intake as soon as possible after treatment. In this process, for cases involving malnutrition or with a history of hepatic encephalopathy, it is also effective to combine the use of enteral nutrients for liver failure (one to two packs) as LES for the improvement of the respiratory quotient and nitrogen balance as well as the maintenance of serum albumin values [16].

Acknowledgments The authors would like to thank Dr. Akinobu Kato (Department of Gastroenterology, Morioka Municipal Hospital) and Dr. Kazuyuki Suzuki (Department of Nutritional Science, Morioka University), for their assistance in creating this article.

References

1. ASPEN Board of Disorders and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr. 2002;26(1 Suppl):65SA–8SA.
2. Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al. ESPEN guidelines on enteral nutrition: liver disease. Clin Nutr. 2006;25:285–94.
3. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol. 2005;3:705–13.
4. Schneeweiss B, Graninger W, Ferenci P, Eichinger S, Grimm G, Schneider B, et al. Energy metabolism in patients with acute and chronic liver disease. Hepatology. 1990;11:387–93.

5. Müller MJ, Lautz HU, Plogmann B, Bürger M, Körber J, Schmidt FW. Energy expenditure and substrate oxidation in patients with cirrhosis: the impact of cause, clinical staging and nutritional state. Hepatology. 1992;15:782–94.
6. Charlton MR. Energy and protein metabolism in alcoholic liver disease. Clin Liver Dis. 1998;2:781–98.
7. Dolz C, Raurich JM, Ibáñez J, Obrador A, Marsé P, Gayá J. Ascites increases the resting energy expenditure in liver cirrhosis. Gastroenterology. 1991;100:738–44.
8. Tajika M, Kato M, Mohri H, Miwa Y, Kato T, Ohnishi H, et al. Prognostic value of energy metabolism in patients with viral liver cirrhosis. Nutrition. 2002;18:229–34.
9. Nishiguchi S, Habu D. Effect of oral supplementation with branched-chain amino acid granules in the early stage of cirrhosis. Hepatol Res. 2004;30S:36–41.
10. Suzuki K, Endo R, Kohgo Y, Ohtake T, Ueno Y, Kato A, et al. Guidelines on nutritional management in Japanese patients with liver cirrhosis from the perspective of preventing hepatocellular carcinoma. Hepatol Res. 2012;42:621–6. https://doi.org/10.1111/j.1872-034X.2012.00990.x.
11. Plauth M, Cabré E, Campillo B, Kondrup J, Marchesini G, Schütz T, et al. ESPEN guidelines on parenteral nutrition: hepatology. Clin Nutr. 2009;28:436–44. https://doi.org/10.1016/j.clnu.2009.04.019. Epub 2009 June.
12. Fukui H, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51:629–50. https://doi.org/10.1007/s00535-016-1216-y. Epub 2016 May 31.
13. Suzuki K, Kato A, Iwai M. Branched-chain amino acid treatment in patients with liver cirrhosis. Hepatol Res. 2004;30S:25–9.
14. Nakaya Y, Okita K, Suzuki K, Moriwaki H, Kato A, Miwa Y, et al. BCAA-enriched snack improves nutritional state of cirrhosis. Nutrition. 2007;23:113–20.
15. Kato A, Suzuki K. How to select BCAA preparations. Hepatol Res. 2004;30S:30–5.
16. Suzuki K. Branched-chain amino acid supplementation during the endoscopic injection sclerotherapy for esophageal varices may be useful for maintenance of nutritional status in patients with liver cirrhosis. Hepatol Res. 2005;32:144–5.

Chapter 20
Endoscopic Treatment of Esophageal Varices: Selection of Treatment Method

Katsutoshi Obara

Abstract In Japan, endoscopic treatment, which includes endoscopic injection sclerotherapy and endoscopic variceal ligation, is the first-line treatment for esophageal varices. However, as both of these methods have their respective pros and cons, individual patient conditions and portal hemodynamics must be fully studied so that an optimal treatment method can be selected for each patient. More precisely, the patient conditions that need to be studied include the residual liver function and the presence of hepatocellular carcinoma. In addition, endoscopic ultrasonography is useful for studying the portal hemodynamics in the immediate surroundings of varices, while three-dimensional computed tomography is useful for studying the overall portal region. Recently, high-resolution imaging of endoscopic ultrasonography has made it possible to evaluate the development of periesophageal veins and perforating veins, which also contributes to the selection of an optimal treatment method.

Keywords Esophageal varices · Endoscopic injection sclerotherapy · Endoscopic variceal ligation · EUS · MDCT

20.1 Introduction

Esophageal variceal bleeding is a life-threatening event; therefore, various treatment methods have been developed to date to prevent it. In Japan, shunt surgery [1] was adopted in the 1930s and 1940s; however, this was replaced by direct surgery (in the form of the Sugiura method) [2] in the 1950s and 1960s because shunt surgery was often accompanied by severe complications such as hepatic encephalopathy and obstruction of the placed shunt. In the 1980s, endoscopic

K. Obara
Department of Advanced Gastrointestinal Endoscopy, Fukushima Medical University, Fukushima, Fukushima, Japan
e-mail: k-obara@fmu.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_20

injection sclerotherapy (EIS) was introduced and adopted by many institutes, initially in the form of the Takase method [3] and subsequently followed by the Suzuki method [4], the Obara method [5], the Ethanol-Thrombin-Polidocanol (ETP) method [6], and the Kitano method [7]. Furthermore, the mucosal fibrosis method (consolidation method) was introduced as a recurrence prevention treatment [8–11]. In 1986, Stiegman et al. [12] introduced endoscopic variceal ligation (EVL), which was easy to perform and safe for the patient, and this method rapidly became popular. Pharmacological therapy and conservative therapy using a Sengstaken-Blakemore (SB) tube may also be applied in some cases. This chapter describes how to select an optimal endoscopic treatment strategy for esophageal varices.

20.2 Indications and Contraindications

20.2.1 Indications

Endoscopic treatment is indicated for bleeding cases (emergency), elective cases with a history of bleeding, and prophylactic cases with varices of size of F2 or larger and red color sign-positive varices regardless of the F-factor according to the general rules for recording endoscopic findings of esophagogastric varices [13–16].

According to the ASGE guidelines [17] and Baveno VI consensus report [18], either nonselective beta-blocker or EVL is recommended for the prevention of an initial bleeding or rebleeding. However, EIS is widely performed and recommended in the evidence-based clinical guidelines in Japan because it yields a significant reduction in initial and recurrent bleeding rates [15, 19–22] coming from high EIS skills of endoscopists. Moreover, some reports overseas also support the efficacy of prophylactic EIS by skillful endoscopists [23–26].

20.2.2 Contraindications

Endoscopic treatment is contraindicated for cases with severe hypoalbuminemia (2.5 g/dL or less), severe platelet depletion (20,000/μL or less), disseminated intravascular coagulopathy, massive ascites retention, severe encephalopathy, or severe renal disorder. EIS using EO is contraindicated in patients with severe hepatic disorders (Child-Pugh C, total bilirubin 4.0 mg/dL or more), where alternative EVL can be performed [16, 27].

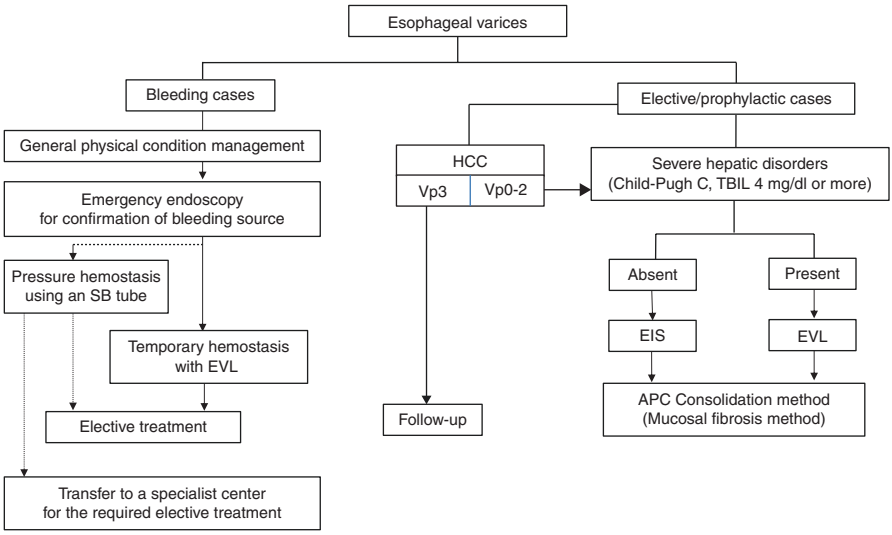


Fig. 20.1 Treatment strategy for esophageal varices based on patient's pathological conditions. Modified from: Obara K, Toyonaga A, Kokubu S. Guidelines for the endoscopic treatment of esophagogastric varices. In: Society for Japanese Gastroenterological Endoscopy editors. Guidelines for Gastrointestinal Endoscopy 3rd ed. Tokyo: Igaku-Shoin; 2006. p. 215–34. [In Japanese]. *SB tube* Sengstaken-Blakemore tube, *EVL* endoscopic variceal injection, *HCC* hepatocellular carcinoma, *EIS* endoscopic injection sclerotherapy, *APC* argon plasma coagulation

20.3 Treatment Strategy Based on the Patient Conditions

Identification of patient conditions is essential for the safe and effective treatment of esophageal varices. Figure 20.1 shows treatment strategy based on the patient's pathological conditions [16].

20.3.1 Cirrhotic Cases Without Severe Hepatic Disorder or Hepatocellular Carcinoma

For bleeding cases, emergency endoscopy should be performed in keeping with the management of the patient's general physical condition to confirm the bleeding source. Once the bleeding source has been confirmed, attempt temporary hemostasis by means of EVL. In the case that EVL is not readily available, use an SB tube to achieve pressure hemostasis, and wait for an endoscopist or transfer the patient to facilities where endoscopic treatment can be performed. After hemostasis is achieved, it is important to perform elective treatment as soon as possible [15, 27].

For the treatment of elective and prophylactic cases, select EIS using EO to obliterate the esophageal varices and their feeding veins, followed by paravariceal injection of aethoxysklerol (AS) to eliminate any small recurrence-prone vessels (EO-AS combination method) [9, 15, 16]. If experienced endoscopists to perform EIS are not readily available, EVL is an alternative. In cases where EIS or EVL is indicated, this should be followed up with consolidation treatment in order to further reduce the risk of recurrence [8, 10, 11, 28].

20.3.2 Severe Hepatic Disorder Cases

For bleeding, prophylactic, and elective cases with severe hepatic disorders, avoid applying EIS using EO whenever possible because it aggravates hepatic disorders, and select EVL followed by EIS using AS (EVL-AS combination method), or perform EIS using EO after the severe hepatic disorder has been cured, and finish off by performing the consolidation method (mucosal fibrosis method) by means of argon plasma coagulation [16, 27].

20.3.3 HCC Complicated Cases

20.3.3.1 Treatment of Esophageal Varices with HCC (Vp 0–2)

This treatment policy can be identical to the one used for cirrhotic cases not complicated by hepatocellular carcinoma (HCC). If EIS using EO is contraindicated because of severe hepatic disorder, apply the EVL-AS combination method, or perform EIS using EO after the severe hepatic disorder has been cured. As such cases Vp 0–2 [29] tend to advance to Vp 3, applying the mucosal fibrosis method (consolidation method), while Vp 0–2 helps prevent acute bleeding due to a sudden rise in portal vein pressure when the disease advances to Vp3 [30, 31].

20.3.3.2 Treatment of Esophageal Varices with HCC (Vp 3)

The first choice for the treatment of acute bleeding in Vp 3 cases is EVL, which provides a favorable hemostatic effect [32].

For the treatment of elective and prophylactic cases, patients should be followed closely without endoscopic treatment. Prophylactic EIS using EO in Vp 3 cases is not only ineffective but can also induce variceal bleeding, which often results in death due to hepatic failure [31]. However, Hayashi et al. reported that in Vp 3 HCC

cases with severe hepatic disorders, the EVL-AS combination method successfully prevented the patients with likely-to-bleed esophageal varices from bleeding to death [33]. In general, however, there is currently no consensus on the applicability of prophylactic endoscopic treatment for esophageal varices with Vp 3 HCC.

20.4 Treatment Strategy Based on Portal Hemodynamics

Endoscopic ultrasonography (EUS) and three-dimensional computed tomography (3D-CT) are useful imaging modalities in the identification of portal vein hemodynamics. Figure 20.2 shows how blood circulation anomalies cause esophagogastric varices [34]. When portal vein pressure increases and obstructs the intrahepatic blood flow, the blood flows backward into collateral circulation routes such as the left gastric vein, posterior gastric vein, and short gastric vein in order to return to the superior vena cava via the

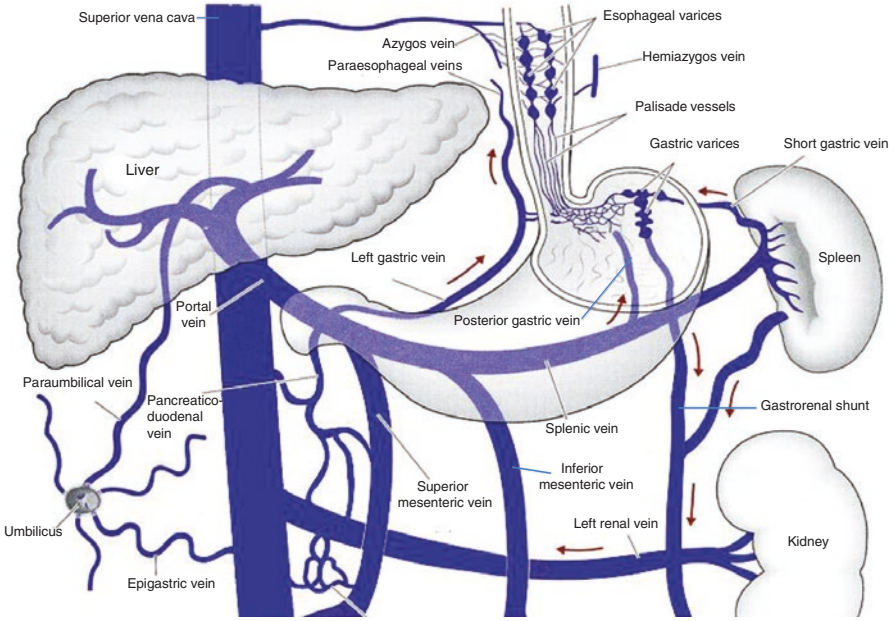


Fig. 20.2 How blood circulation anomalies cause esophagogastric varices. Modified from: Toyonaga A. Pathogenesis and clinical physiology of esophagogastric varices. In: Esophagogastric Varices 3rd ed. Supervised by Obara K and Suzuki H. Tokyo: Nihon Medical Center; 2012: p. 21–8 [In Japanese]. When portal vein pressure increases and obstructs the intrahepatic blood flow, the blood flows backward into collateral circulation routes such as the left gastric vein, posterior gastric vein, and short gastric vein in order to return to the superior vena cava via the azygos vein. As a result, vessels along the route such as the esophageal and gastric wall veins dilate, become tortuous, and finally form esophagogastric varices

azygos vein. As a result, blood vessels along the route such as the esophageal and gastric wall veins dilate, become tortuous, and finally form esophagogastric varices.

It is essential to adopt a treatment technique that takes into consideration the hemodynamics of esophageal varices, so that feeding veins can be identified for obliteration, resulting in prevention of recurrence.

20.4.1 Endoscopic Ultrasonography

EUS is a useful means of performing noninvasive identification of blood routes inside and outside the esophageal and gastric walls. With observation using a 20 MHz ultrasonic miniprobe (UMP), esophageal varices are imaged as a non- or low-echoic lumen in the submucosa. Esophageal varices often communicate with the periesophageal veins (Peri-v) and paraesophageal veins (Para-v) through perforating veins (Figs. 20.3 and 20.4) [15, 35, 36]. In the mid-esophagus, an azygos vein is observed as the drainage route for esophageal varices. Peri-v and perforating veins are related to the development of esophageal varices.

The recurrence frequency is high when the remains of Peri-v or large perforating veins are observed during UMP examination after treatment [37] (Table 20.1); therefore, it is important to obliterate Peri-v and perforating veins during the initial EIS. Figure 20.5 is an autopsied example of ruptured esophageal varix where palisade vein disappeared but periesophageal veins remained after treatment supplying blood to the varix through the perforating veins. If Peri-v and/or perforating veins remain after treatment, the consolidation method should be additionally employed

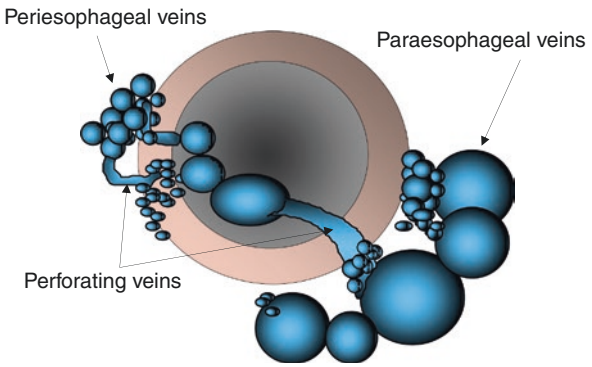


Fig. 20.3 Esophageal collaterals observed using endoscopic ultrasound. Modified from: Irisawa A, Saito A, Obara K, Shibukawa G, Takagi T, Shishido H, et al. Endoscopic recurrence of esophageal varices is associated with the specific EUS abnormalities: Severe periesophageal collateral veins and large perforating veins. Gastrointest Endosc. 2001;53:77–84

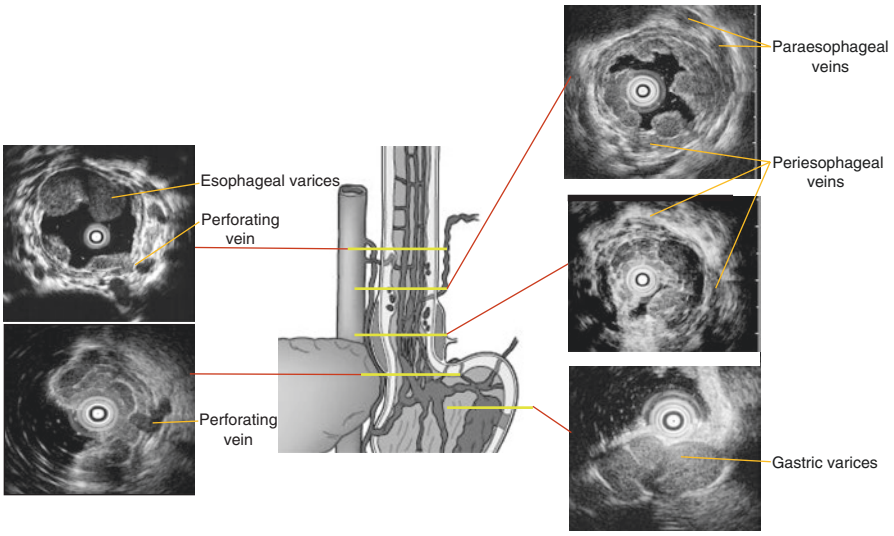


Fig. 20.4 Esophageal collaterals observed using endoscopic ultrasound. Fill the stomach and esophagus with deaerated water and observe the region from the cardia to the lower esophagus

Table 20.1 Posttreatment EUS findings on recurrent and nonrecurrent esophageal varices

EUS findings	Recurrence (10 cases)	Non-recurrence (28 cases)	*p*-value
Posttreatment follow-up (months)	10.9 ± 5.1	11.3 ± 1.0	NS
Peri-v			
Severe (%)	80	7.1	0.001
Mild (%)	20	92.9	
Para-v			
Severe (%)	60	42.9	NS
Mild (%)	40	57.1	
Perforating vein			
Rate of incidence (%)	90	21.4	0.001
No. of incidence	1.30 ± 0.67	0.21 ± 0.42	0.001
Diameter (mm)	2.00 ± 1.15	0.32 ± 0.67	0.001

Modified from: Irisawa A, Saito A, Obara K, Shibukawa G, Takagi T, Shishido H, et al.: Endosopic recurrence of esophageal varices is associated with the specific EUS abnormalities: Severe peri-esophageal collateral veins and large perforating veins. Gastrointest Endosc. 2001;53:77–84
EUS endoscopic ultrasonography, *Peri-v* periesophageal veins, *Para-v* paraesophageal veins

to prevent a recurrence. Furthermore, when performing EIS, as the perforating vein acts as a shunt to the outside of the esophageal varices, appropriate measures need to be taken to prevent the sclerosant from leaking into the general circulation in cases involving large perforating veins.

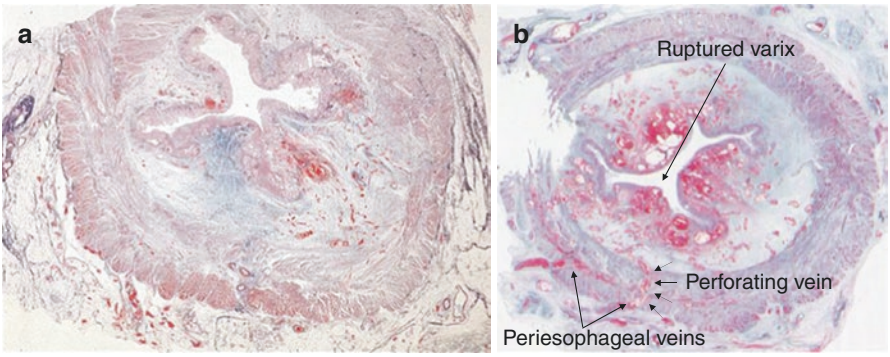


Fig. 20.5 Recurrence of esophageal varix with remaining Peri-v. This case is an example of esophageal varix relapse after endoscopic injection sclerotherapy. The palisade vein had disappeared at the esophagogastric junction (**a**), but the bleeding resumed from the esophageal varix due to the Peri-v from which blood was transferred to the esophageal varix via the perforating vein, resulting in the death of the patient. This sample was taken from the subsequent pathologic autopsy (**b**). *Peri-v* periesophageal veins

Nakamura et al. [38] classified the pattern of variceal blood flow detected using 3D-EUS into four types (Fig. 20.6). In type 1 patients without Para-v, the cumulative recurrence-free rates at 24 months after treatment were 28.9% for the ligation group and 71.1% for the sclerotherapy group ($p < 0.05$), while in type 2–4 patients with Para-v, the cumulative recurrence-free rates did not significantly differ between the two groups regardless of the presence or absence of perforating veins. Hino et al. [39] examined the anterior and posterior branches of the left gastric vein using a color Doppler EUS and reported that recurrence occurred less often in patients with well-developed Para-v from posterior branches of the left gastric vein after the endoscopic treatment.

As described above, a detailed examination of the hemodynamics of the esophageal varices and their surrounding veins can facilitate safe and effective tailor-made treatment in patients with esophageal varices by preventing adverse events due to leakage of EO. Moreover, such an examination also contributes to the selection of an optimal treatment strategy because understanding the development of extravariceal veins allows endoscopists to predict whether treatment with EVL would be as effective as treatment with EIS in each particular case.

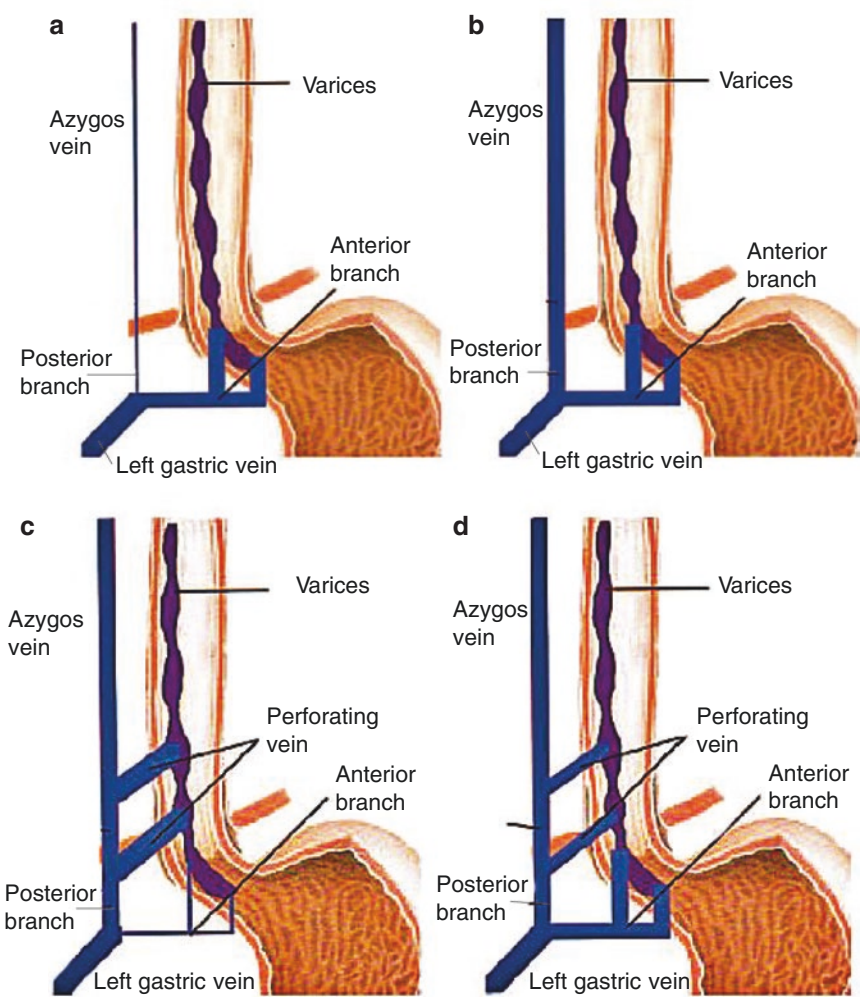


Fig. 20.6 Classification of vascular patterns based on 3D endoscopic ultrasonographic findings. Modified from: Nakamura S, Murata Y, Mitsunaga A, Oi I, Hayashi N, Suzuki S: Hemodynamics of esophageal varices on three-dimensional endoscopic ultrasonography and indication of endoscopic variceal ligation. 15; 289–97, 2003. (**a**) Type 1: cardial-inflow type without paraesophageal veins. (**b**) Type 2: cardial-inflow type with paraesophageal veins. (**c**) Type 3: azygos-perforating pattern. (**d**) Type 4: complex pattern. *3D* three-dimensional, *PEVs* paraesophageal veins, *LGV* left gastric vein, *PGV* posterior gastric vein, *SGV* short gastric vein

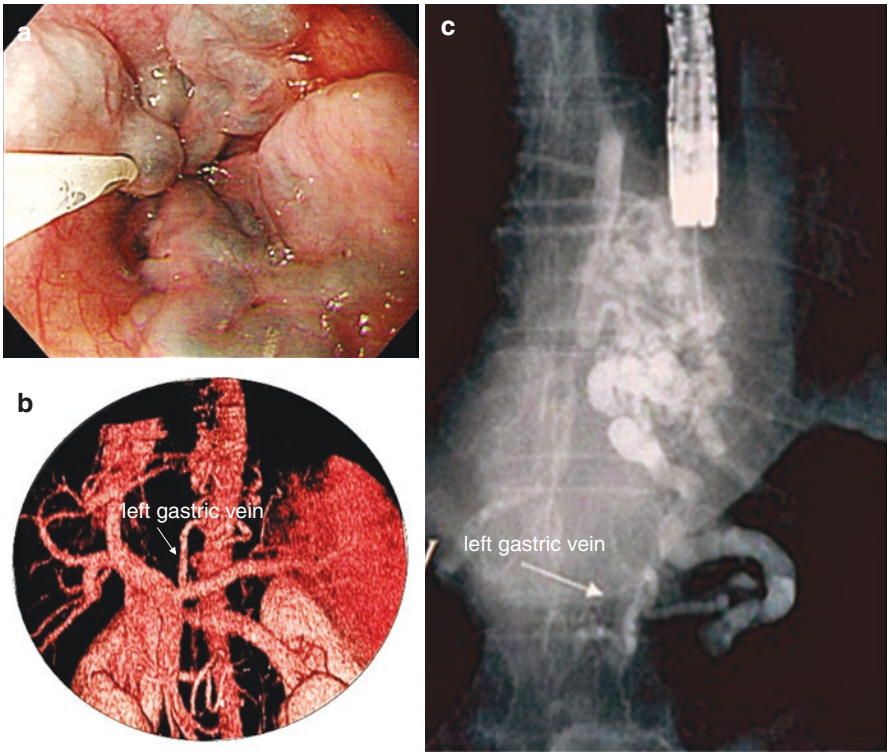


Fig. 20.7 Images of the blood supply routes before and during EO injection. (**a**) The endoscopic findings were *Lm, F2, Cb, RC1 (red wale marking). The esophageal varices were punctured, and 5% ethanolamine oleate was injected. (**b**) The 3D-CT image before the treatment showed that the blood was supplied via the left gastric vein. (**c**) The contrast image of the varices during treatment showed the same blood supply route and esophageal varices as in the 3D-CT image (**b**). *According to the recording rules of esophageal varices in [13, 14]. *3D-CT* three-dimensional computed tomography, *RC* red color sign

20.4.2 Three-Dimensional Computed Tomography

3D-CT is useful for identifying the degree of development of blood supply or collateral blood routes or the presence of a high-risk extraesophageal shunt [15, 40, 41]. This examination method can replace abdominal angiography. As 3D-CT before treatment can identify the blood supply routes, it can be used to estimate the safest and most effective range of EO injections leading to recurrence prevention (Fig. 20.7). It also makes it possible to identify a high-risk extraesophageal shunt before treatment (Fig. 20.8).

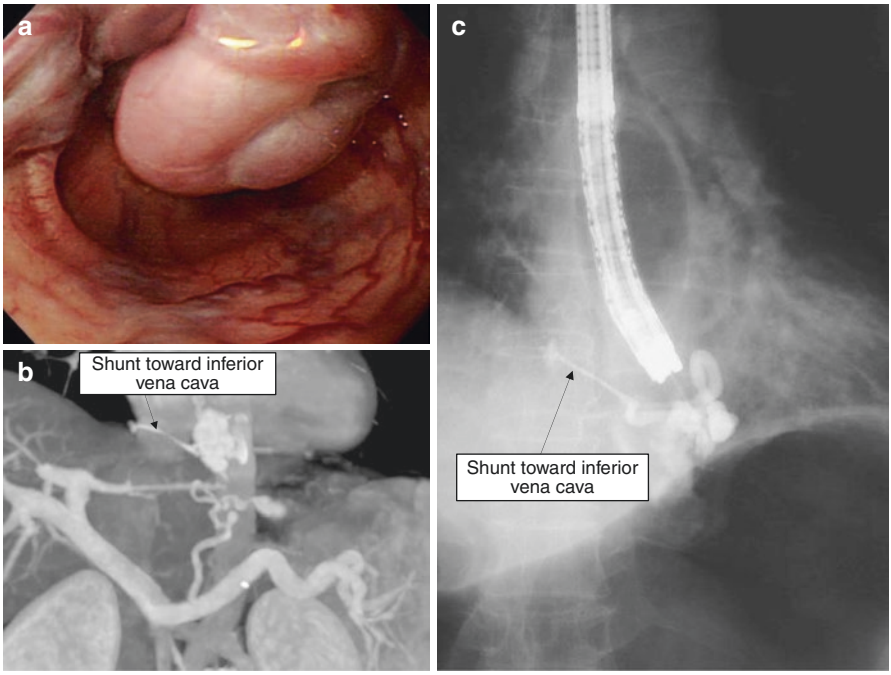


Fig. 20.8 3D-CT findings and contrast imaging of extraesophageal shunt. (**a**) Large esophageal varices observed using endoscopy. (**b**) A high-risk extraesophageal shunt identified using 3D-CT. (**c**) Variceal contrast imaging also showed the same extraesophageal shunt as shown in (**b**) before the treatment. *3D-CT* three-dimensional computed tomography

20.5 Conclusion

In order to select a safe and effective endoscopic treatment strategy for cirrhotic patients with esophageal varices, it is essential to study the patients' medical conditions such as their bleeding history, hepatic reserve, and presence of HCC, and to evaluate their portal vein hemodynamic state using EUS and 3D-CT. In Japan, EVL is the first choice for bleeding cases, while EIS is selected for prophylactic and elective cases in patients without severe hepatic disorder or HCC (Vp 3,4). Each endoscopic treatment results largely depend on the endoscopists' skill; therefore, it is very important to improve techniques of EIS or EVL to achieve an optimal treatment effect.

References

1. Kimoto S, Sugie S. Diagnosis and treatment of portal hypertension. Nihon Geka Gakkai Zasshi (J Jpn Surg Soc). 1956;57:1097–103. [In Japanese].
2. Sugiura M, Ichihara S, Nomura M, et al. Surgical treatment of portal hypertension. Jpn Med J. 1970;2417:7–14. [In Japanese].
3. Takase Y, Iwasaki Y, Haebaru H, et al. Endoscopic injection therapy of esophageal varices using fiberscopes. Prog Dig Endosc. 1978;12:105–8. [In Japanese].
4. Suzuki H, Nagao F. Endoscopic injection sclerotherapy: procedures, indications and outcomes. Seijinbyo to Seikatsushukanbyo (J Adult Dis). 1981;12:2307–11. [In Japanese].
5. Obara K, Masaki M, Sakamoto H, Iwasaki K, Mitsuhashi H, Orikasa K, et al. Studies on prognosis of patients with esophageal and gastric varices treated with injection sclerotherapy using EO or EO-AS combination method. Gastroenterol Endosc. 1987;29:2232–6. [In Japanese with English abstract].
6. Makuuchi H, Tanaka Y, Sugiura K, et al. Endoscopic injection sclerotherapy for esophagogastric varices: ETP method and prognosis. Stomach Intestine. 1985;20:497–505. [In Japanese].
7. Kitano S, Koyanagi N, Iso Y, Higashi H, Sugimachi K. Prevention of recurrence of esophageal varices after endoscopic injection sclerotherapy with ethanolamine oleate. Hepatology. 1987;7:810–5.
8. Deguchi H, Kato J, Maeda Y, Moribata K, Shingaki N, Niwa T, et al. Argon plasma coagulation is effective for prevention of recurrent esophageal varices after endoscopic injection sclerotherapy: single-center case-control study. Dig Endosc. 2016;28:42–9. https://doi.org/10.1111/den.12538.
9. Obara K, Ohira H, Sakamoto H, Iwasaki K, Mitsuhashi M, Suzuki S, et al. A new method of sclerotherapy for esophagogastric varices: EO-AS combination method followed by mucosa-fibrosis with AS. Gastroenterol Endosc. 1981;31:2977–81. [In Japanese with English abstract].
10. Obara K, Kojima T, Irisawa A, Watanabe S, Kuwana T, Kogure A, et al. A new method of sclerotherapy for esophageal varices: EO-AS combination method followed by mucosa-fibrosing with laser. Gastroenterol Endosc. 1994;36:716–21. [In Japanese with English abstract].
11. Nakamura S, Mitsunaga A, Murata Y, Suzuki S, Hayashi N. Endoscopic induction of mucosal fibrosis by argon plasma coagulation (APC) for esophageal varices: a prospective randomized trial of ligation plus APC vs. Ligation alone. Endoscopy. 2001;33(3):210–5.
12. Stiegmann GV, Goff JS, Sun JH, Wilbon S. Endoscopic elastic band ligation for active variceal hemorrhage. Am Surg. 1989;55(2):124–8.
13. Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition.). Dig Endosc. 2010;22:1–9. https://doi.org/10.1111/j.1443-1661.2009.00929.x.
14. The Japan Society for Portal Hypertension. The general rules for study of portal hypertension. 3rd ed. Tokyo: Kanehara & Co., Ltd; 2013. [In Japanese].
15. Fukui H, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51:629–50. https://doi.org/10.1007/s00535-016-1216-y.
16. Obara K, Toyonaga A, Kokubu S. Guidelines for the endoscopic treatment of esophagogastric varices. In: Society for Japanese Gastroenterological Endoscopy, editor. Guidelines for gastrointestinal endoscopy. 3rd ed. Tokyo: Igaku-Shoin; 2006. p. 215–34. [In Japanese].
17. The American Society for Gastrointestinal Endoscopy. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc. 2014;80(2):221–7.
18. de Franchis R, Baveno IV Faculty. Expanding consensus in portal hypertension. Report of the Baveno VI consensus workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–52.
19. Gotoh Y, Iwakiri R, Sakata Y, Koyama T, Noda T, Matsunaga C, et al. Evaluation of endoscopic variceal ligation in prophylactic therapy for bleeding of oesophageal varices: a prospective, controlled tiral compared with endoscopic injection sclerotherapy. J Gastroenterol Hepatol. 1999;14(3):241–4.

20. Ogusu T, Iwakiri R, Sakata H, Matsunaga K, Shimoda R, Oda K, et al. Endoscopic injection sclerotherapy for esophageal varices in cirrhotic patitents without hepatocellular carcinoma: a comparison of longterm survival between prophylactic therapy and emergency therapy. J Gastroenterol. 2003;38(4):361–4.
21. Naritaka Y, Shimakawa T, Isohata N, Asaka S, Konno S, Murayama M, et al. Long-term results of endoscopic injection sclerotherapy in 602 patients with esophageal varices. Hepatogastroenterology. 2008;55(88):2096–102.
22. Iso Y, Kawanaka H, Tomikawa M, Matsumata T, Kitano S, Sugimachi K. Repeated injection sclerotherapy is preferable to combined therapy with variceal ligation to avoid recurrence of esophageal varices: a prospective randomized trial. Hepatogastroenterology. 1997;44:467–71.
23. Westaby D, Poison RJ, Gimson AE, Hayes PC, Hayllar K, Williams R. A controlled trial of oral propranolol compared with injection sclerotherapy for the long-term management of varieal bleeding. Hepatology. 1990;11:353–9.
24. Svoboda P, Kantorova OJ, Kozumplik L, Marsova J. A prospective randomized controlled trial of sclerotherapy vs ligation in the prophylactic treatment of high-risk esophageal varices. Surg Endosc. 1999;13(6):580–4.
25. Krige JE, Bornman PC, Goldberg PA, Terblanche J. Variceal rebleeding and recurrence after endoscopic injection sclerotherapy: a prospective evaluation in 204 patients. Arch Surg. 2000;135(11):1315–22.
26. Krige JE, Kotze UK, Bornman PC, Shaw JM, Klipin M. Variceal recurrence, rebleeding, and survival after endoscopic injection sclerotherapy in 287 alcoholic cirrhotic patients with bleeding esophageal varices. Ann Surg. 2006;244(5):764–70.
27. Obara K. Endoscopic EV treatment. Endoscopic treatment of esophagogastric varices. Tokyo: Narunia Inc.; 2016. p. 21–7.
28. The Japanese Society of Gastroenterology. Evidence-based clinical practice guidelines for liver cirrhosis 2015. 2nd ed. Tokyo: Nankodo Co., Ltd.; 2015. p. 78–9. [In Japanese].
29. The Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer, second English edition. Tokyo: Kanehara & Co., Ltd; 2003.
30. Akahoshi T, Tomikawa M, Tsutsumi N, Hshizume M, Maehara Y. Merits of prophylactic sclerotherapy for esophageal varices concomitant unresectable hepatocellular carcinoma: prospective randomized study. Dig Endosc. 2014;26:172–7.
31. Murashima N, Arase Y, Ikeda K, Chayama K, Saitoh S, Suzuki Y, et al. Endoscopic regression and evaluation of injection sclerotherapy for esophageal varices in case of hepatocellular carcinoma with portal vein invasion. Gastroenterol Endosc. 1996;38(10):2379–85. [In Japanese with English abstract].
32. Kawai T, Yashima Y, Sugimoto T, Sato T, Kanda M, Endo N, et al. Emergency endoscopic variceal ligation following variceal rupture in patients with advanced hepatocellular carcinoma and portal vein tumor thrombosis: a retrospective study. World J Surg Oncol. 2016;14:52. https://doi.org/10.1186/s12957-016-0802-z.
33. Hayashi S, Saeki S. Clinical evaluation of endoscopical treatment for esophago-gastric varices in patients with tumor invasion in the portal vein trunk or first portal branches associated with hepatocellular carcinoma. Jpn J Port Hypertens. 1999;5:183–8. [In Japanese with English abstract].
34. Toyonaga A. Pathogenesis and clinical physiology of esophagogastric varices. In: Esophagogastric varices. 3rd ed. Supervised by Obara K and Suzuki H. Tokyo: Nihon Medical Center; 2012. p. 21–8. [In Japanese].
35. Irisawa A, Obara K, Sato Y, Saito A, Takiguti F, Shishido H, Sakamoto H, et al. EUS analysis of collateral veins inside and outside the esophageal wall in portal hypertension. Gastrointest Endosc. 1999;50:374–80.
36. Obara K, Irisawa A, Sato Y. Usefulness of EUS in portal hypertension with esophageal varices. Dig Endosc. 2004;16(Suppl 2):S168–72.
37. Irisawa A, Saito A, Obara K, Shibukawa G, Takagi T, Shishido H, et al. Endosopic recurrence of esophageal varices is associated with the specific EUS abnormalities: severe periesophageal collateral veins and large perforating veins. Gastrointest Endosc. 2001;53:77–84.

38. Nakamura S, Murata Y, Mitsunaga AI, Hayashi N, Suzuki S. Hemodynamics of esophageal varices on three-dimensional endoscopic ultrasonography and indication of endoscopic variceal ligation. Dig Endosc. 2003;15:289–97.
39. Hino S, Kakutani H, Ikeda K, Uchiyama Y, Sumiyama K, Kuramochi A, et al. Hemodynamic assessment of the left gastric vein in patients with esophageal varices with color doppler EUS: factors affecting development of esophageal varices. Gastrointest Endosc. 2002;55(4):512–7.
40. Shimizu T, Namba R, Matsuoka T, Tabuchi K, Ymamoto K, Umesugi Y, et al. Esophageal varices before and after endoscopic variceal ligation: evaluation using helical CT. Eur Radiol. 1999;9:1546–9.
41. Mifune H, Akaki S, Ida K, Sei T, Kanazawa S, Okada H. Evaluation of esophageal varices by multidetector-row CT: correlation with endoscopic 'red color sign'. Acta Med Okayama. 2007;61:247–54.

Chapter 21
Endoscopic Treatment of Esophageal Varices: Obara Method

Katsutoshi Obara

Abstract Endoscopic treatment is the first choice for treating esophageal varices in Japan. In particular, the Obara method, which is known as the ethanolamine oleate (EO)-Aethoxysklerol (AS) combination method, is widely performed as it contributes to a low risk of recurrence. Inject 5% EO into all the esophageal varices and their feeding veins under fluoroscopy until they can be imaged on a fluoroscopy monitor. After the esophageal varices are obliterated using the EO method, inject 1% AS into the obliterated varices and their surrounding mucosa so that shedding of the obstructed esophageal varices and sclerosis of the esophageal wall by fibrosis can be expected. The Obara method is an extremely useful procedure for preventing recurrence by completely eradicating esophageal varices.

Keywords Esophageal varices · Obara method · EO-AS combination method
Ethanolamine oleate · Aethoxysklerol

21.1 Introduction

A variety of treatment methods have been adopted for the endoscopic treatment of esophageal varices. Ethanolamine oleate (EO) was first employed in the treatment of esophageal varices in 1946 by Trolle et al. [1], and in Japan, Takase et al. introduced endoscopic injection sclerotherapy (EIS) using 5% EO (the EO method or the Takase method) in 1978 [2]. And Suzuki et al. established a unique intra- and paravariceal combined injection technique with 1% Aethoxysklerol (AS), the so-called Suzuki method, in 1981 [3]. In those days, the Takase method was validated as effective; however, it was associated with a number of complications, while the Suzuki method was found to be safer but

K. Obara
Department of Advanced Gastrointestinal Endoscopy, Fukushima Medical University, Fukushima, Fukushima, Japan
e-mail: k-obara@fmu.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_21

less effective than the Takase method. Therefore, in 1987, Obara et al. introduced the EO-AS combination method, the so-called Obara method, in 1987, which adopted the advantages of both of these previous methods in order to enhance their efficacy and safety [4].

Evidence-based guidelines for liver cirrhosis 2015 recommend that EIS should be used for the treatment of esophageal varices because both recurrence rates and bleeding (including rebleeding) rates are lower in patients treated with EIS compared with those in patients treated with endoscopic variceal ligation (EVL) resulting in the effective prevention of recurrence of esophageal varices (Recommendation grade 1, Evidence level A) [5–7].

This chapter describes the action mechanisms of sclerosing agents used in the Obara method and its treatment procedures.

21.2 Action Mechanism of Sclerosing Agents

21.2.1 Ethanolamine Oleate (EO)

EO is an anionic surfactant that was originally used as a leather-softening agent. In our institute in the 1980s, the action mechanism of EO was intensively studied using a dog so that it could be clinically applied in an optimal manner [8]. EO poses vascular endothelial cell damaging action [9–11], thrombus formation action [12–14], hemolytic action [15–18], tissue-damaging action [19], and/or effects on the circulatory system such as lowering the blood pressure or shock, the main mechanism for which has traditionally been thought to be a decline in cardiac output coupled with bradycardia.

21.2.2 Aethoxysklerol (AS)

AS is a 1% solution of the anionic surfactant polidocanol. In our institute, AS was injected around the auricular veins of a rabbit, and changes in the tissue were studied over time [8]. Injection of AS on the periphery of small veins results in ulceration due to AS's tissue-damaging action. This causes the small veins to develop necrosis and fall off together with the ulcer or the periphery of the small veins to develop a dense coating of fibrous tissues. As the ulcer produced by AS is shallower than that formed by EO or absolute ethanol (ET) [19], there is little risk of perforation. Moreover, the fibrosis occurs very quickly and is similar in degree to EO and ET. This makes AS the optimum sclerosing agent for injection on the periphery of esophageal varices [20].

21.2.3 Efficacy of EO Method

Histological examination of an autopsied esophagus (Fig. 21.1) [8] in a patient with terminal hepatocellular carcinoma and imminent signs of esophageal variceal rupture 1 week after treatment using the EO method showed that the two varices

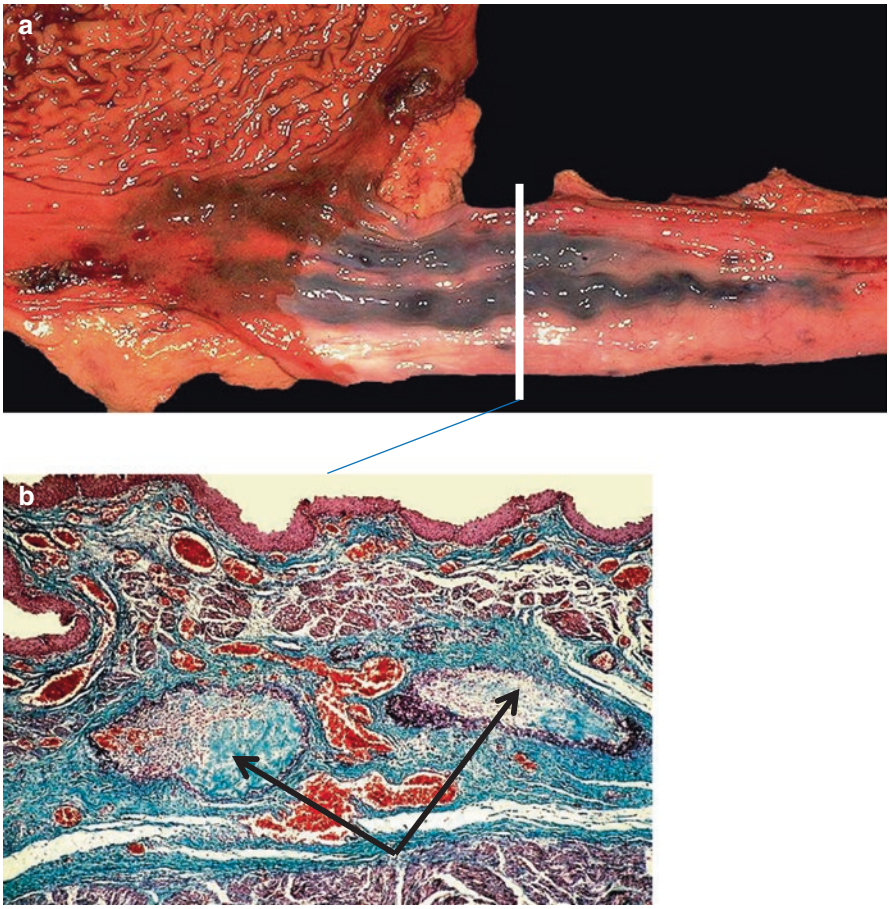


Fig. 21.1 Pathological findings 1 week after the treatment with the EO method (autopsied case). (**a**) This image shows the autopsied esophagus and stomach of a terminal HCC case 1 week after a procedure using the EO method. Two lines of esophageal varices exhibiting thromboses are visible macroscopically. *HCC* hepatocellular carcinoma, *EO* ethanolamine oleate. (**b**) This is a histopathological image of the lower esophagus. Totally occluded thromboses are observed in two esophageal varices in which EO was injected, showing the effects of the EO method (black arrows). However, the growth of small recurrence-prone blood vessels of various sizes is observed in the surrounding region

into which EO had been injected had developed totally obliterated thrombi, indicating the efficacy of the EO method. However, the growth of small blood vessels of various sizes was observed in their vicinity. These vessels are called recurrence-prone vessels due to the high likelihood of their giving rise to a recurrence. In order to prevent a recurrence, it is useful to eliminate these vessels by employing the AS method after completing the EO method [4].

21.3 Obara Method Procedures

The Obara method is the EIS treatment for recurrence prevention, in which the Takase method and the Suzuki method are applied (Fig. 21.2) [4].

21.3.1 EO Method

This technique is employed to obliterate the esophageal varices and their blood supply routes by tracing them under fluoroscopy. With intravenous injection, a puncture is started in the largest varix. If the sizes of the varices are similar, the puncture is started in the varix that displays the most advanced red color (RC) signs [21, 22]. If a clear red plug or white plug is found with an elective case, that

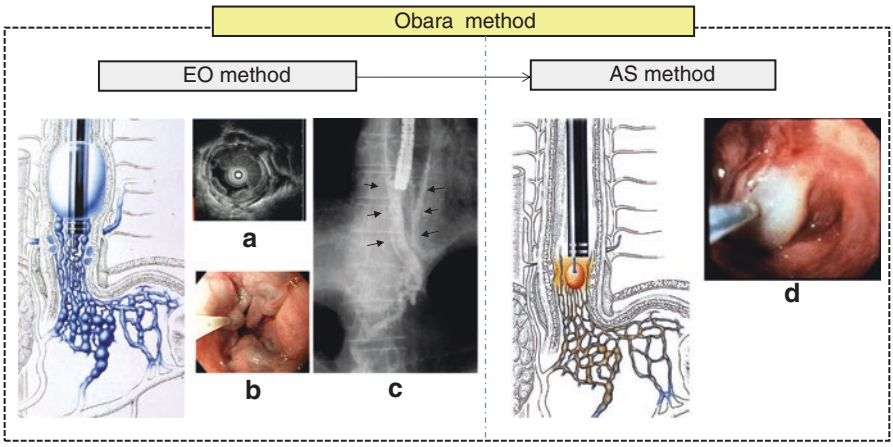


Fig. 21.2 Obara method (EO-AS combination method). (**a**) EUS findings. The varices are observed as low-echoic lumen images in the submucosal layer. (**b**, **c**) Puncture from the 7 o'clock direction, inject enough 5% EO into the esophageal varices and the blood supply route to produce an occlusive thrombosis. *EUS* endoscopic ultrasonography, *EO* ethanolamine oleate, *AS* aethoxysklerol. (**d**) Inject 1% AS into the mucosa surrounding the small blood vessels that remain after the EO method has been performed in order to completely eradicate the varices by necrosis and drop-off

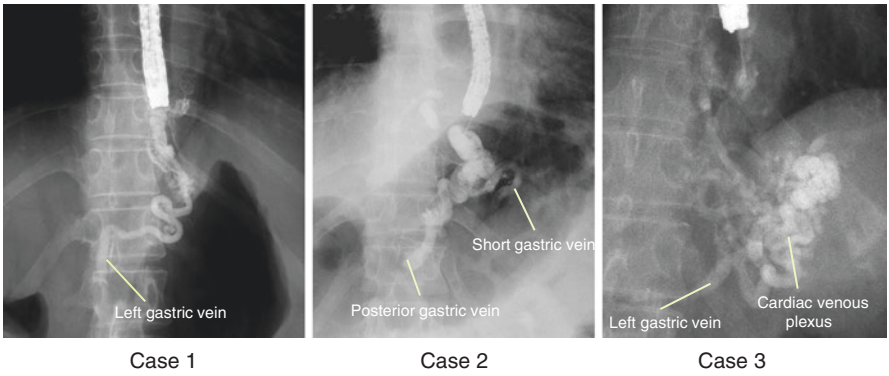


Fig. 21.3 Blood supply routes observed during injection sclerotherapy

specific varix must be treated first. When enough EO has been injected, EO injection should be stopped while confirming that the blood supply routes are being imaged (Fig. 21.3) [4, 8, 23].

21.3.1.1 Pipeline Varix

Kumagai et al. [24] proposed that a giant esophageal varix connected to a cardiac varix should be called a "giant-tree-type varix," while Toyonaga [25] suggested the term "pipeline varix" based on portal vein contrast imaging. As blood flows directly from the left gastric vein (LGV) to the varix without passing through the palisade veins, a large volume of blood flows rapidly, with the result that the high frequency of extraesophageal shunt complications makes such varices even more resistant to treatment.

Block the blood flow securely with a 6 cm balloon, and confirm the presence of a shunt and the quantity of blood flow by means of variceal contrast imaging using a contrast agent. If the contrast imaging is successful enough that the LGV can be imaged, inject EO into the LGV. If the contrast imaging is unsuccessful and a shunt is present, refer to the Sect. 21.3.1.2. "Giant-tree"-type pipeline varices are generally difficult to treat with just one EO session; therefore, a second EO session is often performed 1 week later in order to achieve complete obliteration.

21.3.1.2 Esophageal Varices with a High-Risk Extraesophageal Shunt

When performing the EO method, make sure that EO flows into the blood supply routes and not into the lung, the heart, or the whole body. Should this occur, stop the EO injection immediately, taking into account the presence of high-risk shunts, which are portopulmonary shunts in the portopulmonary venous anastomosis (PPVA) and the inferior vena cava (IVC) (Fig. 21.4) [26–29]. EO flowing from the

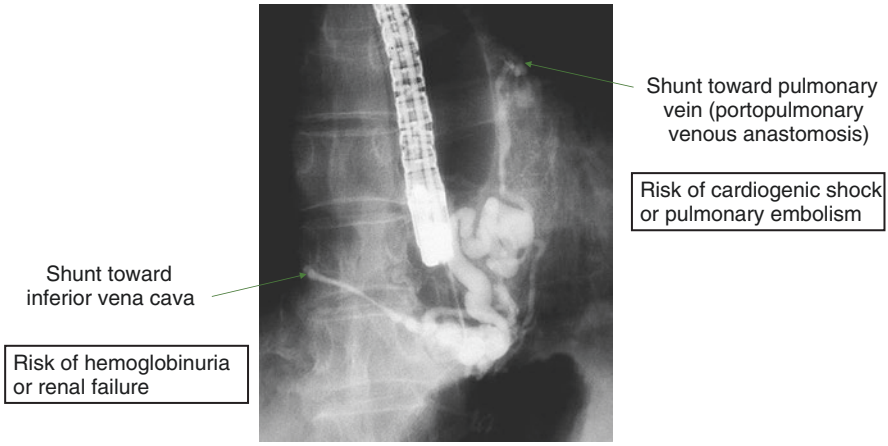


Fig. 21.4 A high-risk extraesophageal shunt case

PPVA into the pulmonary veins could cause a shock or a pulmonary embolism, and EO flowing into the IVC poses the risk of inducing hemoglobinuria or renal failure.

Image the shunt with a contrast agent, and, if the contrast imaging is defective, administer 0.5–1 mL of ET intermittently (total dose, 3 mL or less); wait for 1–2 min, and reattempt contrast imaging (the ET method) [10, 26]. If it can occlude the shunt and the blood supply routes are imaged, inject EO into the blood supply routes. If the blood supply routes cannot be imaged by contrast imaging, withdraw the needle, and, if bleeding occurs, pressurize the bleeding point for 2–3 min with a 6 cm balloon for hemostasis. After hemostasis, apply the EO method to the other varices. Try to treat the problematic varices again after 1 week. If the ET method conducted 1 week later is still ineffective, confirm the shunted vessel with a 20 MHz ultrasonic miniprobe (UMP), and ligate the perforating section with a rubber O-ring. Then puncture the varix on the anal side of the ligated lesion, and obliterate the blood supply routes with EO (the selective EVL-EO combination method) [30].

UMP findings are useful for identifying high-risk shunts before treatment. If the diameter of the perforating vein observed with a UMP is smaller than 3 mm, the EO method is effective. If it is 3–5 mm, ET is effective (Fig. 21.5). However, if the diameter is bigger than 5 mm, the ET method is ineffective; therefore, the selective EVL-EO combination method should be used [26].

21.3.2 AS Method

The aims of the AS method are to cause the thrombosed esophageal varices produced by the EO method to fall off and to eliminate any remaining small blood vessels (recurrence-prone vessels). It is effective to inject 2 mL of AS per point so

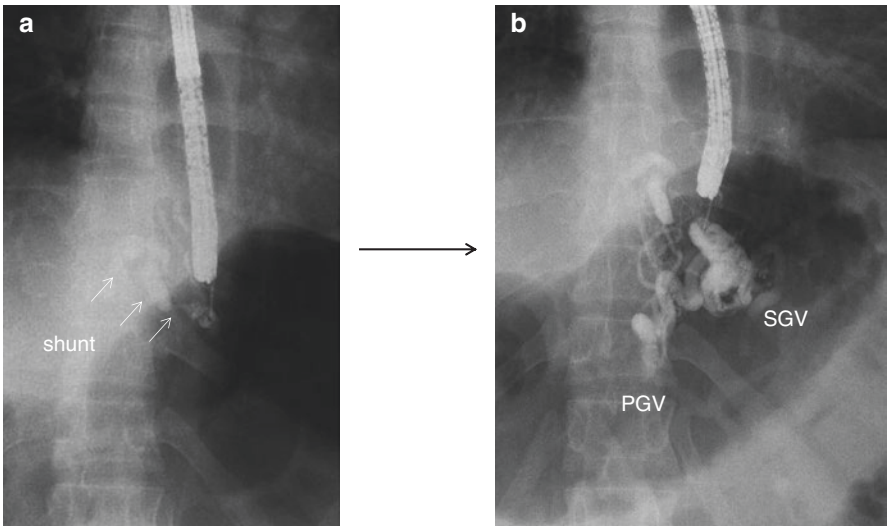


Fig. 21.5 Treatment procedures for esophageal varices with an extraesophageal shunt. (**a**). The shunt diameter of this varix as measured with EUS was 4.2 mm. As the injected contrast agent flowed out to the shunt (inferior vena cava), the blood supply routes were not imaged. *EUS* endoscopic ultrasonography. (**b**) After injecting 1 mL of ET and waiting for 2 min, contrast imaging was reattempted. As this succeeded in imaging the blood supply routes, EO was injected until the blood supply routes (PGV and SGV) were obliterated. *ET* absolute ethanol, *EO* ethanolamine oleate, *PGV* posterior gastric vein, *SGV* short gastric vein

that it bulges from inside the mucosa. Injection in the submucosa is ineffective because AS spreads widely, and injection of a large amount in the muscle layer poses a risk of mediastinitis or esophageal perforation. The total amount of AS should be limited to within 20 mL [23].

21.4 Treatment Outcomes

With the Obara method, the accumulated nonrecurrence rates were 83.2% after 1 year, 68.1% after 3 years, and 66.0% after 5 years. The recurrent cases were F1–F2 esophageal varices with RC-positive, and bleeding occurred in about 10% of these cases (Fig. 21.6) [4, 8, 31]. All recurrent cases required inpatient treatment. Deguchi et al. compared the cumulative recurrence rates between the EO-AS combination method (the Obara method) only and EO-AS combination method followed by APC consolidation and reported that the recurrence rates were 29.0% after 1 year and 34.7% after 2 years in cases without the consolidation method and 9.7% after 1 year and 11.3% after 2 years in cases with the consolidation method ($p = 0.013$) [32]. Accordingly, the Obara method has been shown to be effective in preventing recurrence, and applying the mucosal fibrosis method (consolidation

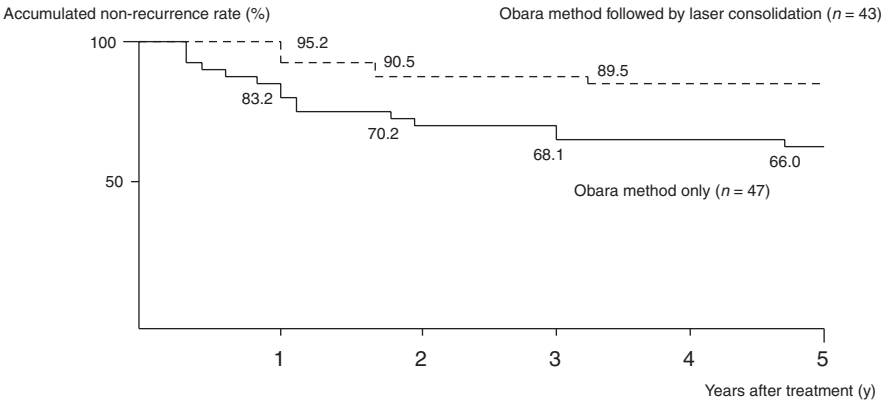


Fig. 21.6 Cumulative nonrecurrence rates in patients treated using the Obara method followed by laser consolidation. Quoted from: Obara K [31]

method) has been shown to further reduce the recurrence rates (please see Chap. 25).

21.5 Complications

The precautions to be taken when employing the EO method are to avoid allowing EO to flow into the portal vein (the inflow of a large amount of EO carries with it the risk of portal vein thrombus or hepatic failure due to endothelial cell damage), limit the total EO injection amount to within 0.4 mL/kg (excessive administration may induce cardiogenic shock) [26], minimize the outflow to the rest of the body (otherwise, the hemolysis action of EO may cause hemoglobinuria or renal failure), and reduce extravascular EO leaks outside the blood vessel to 2 mL or less (otherwise, the strong tissue-damaging action of EO may cause esophageal ulceration and/or perforation).

As action mechanisms of EO are well known these days, critical complications are rarely found, while the AS method was originally a safe procedure with few complications [26, 31].

21.6 Conclusion

With the EO method only, recurrence of the varices cannot be prevented in a satisfactory manner. Therefore, it is extremely important to additionally apply AS method after the esophageal varices and their feeding veins have been obliterated. The Obara method for treating esophageal varices is a basic procedure of EIS

requiring comparatively more skill and experience than those required for EVL. However, with experienced endoscopists it is an essential treatment method on account of its improved patient safety and its efficacy in preventing recurrence for a long time.

References

1. Trolle E, Trolle D. Treatment of oesophageal varices by injection of sclerosing agents through oesophagoscope in splenectomized patients suffering from splenic phlebostenosis (splenic anemia): a case with autopsy. Acta Chir Scand. 1946;94:385–96.
2. Takase K, Iwasaki Y, Haebaru H, et al. Endoscopic injection therapy of the esophageal varices using fiberscopes. Prog Dig Endosc. 1978;12:105–8. [In Japanese].
3. Suzuki H, Nagao H. Endoscopic injection sclerotherapy: procedures, indications and outcomes. J Adult Dis. 1981;12:2207–311. [In Japanese].
4. Obara K, Masaki M, Sakamoto H, Iwasaki K, Mitsuhashi H, Orikasa K, et al. Studies on prognosis of patients with esophageal and gastric varices treated with injection sclerotherapy using EO or EO-AS combination method. Gastroenterol Endosc. 1987;29:2232–6. [In Japanese with English abstract].
5. Fukui H, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51:629–50. https://doi.org/10.1007/s00535-016-1216-y.
6. Gotoh Y, Iwakiri R, Sakata Y, Koyama T, Noda T, Matsunaga C, et al. Evaluation of endoscopic variceal ligation in prophylactic therapy for bleeding of oesophageal varices: a prospective, controlled trial compared with endoscopic injection sclerotherapy. J Gastroenterol Hepatol. 1999;14(3):241–4.
7. Svoboda P, Kantorova I, Ochmann J, Kozumplik L, Marsova J. A prospective randomized controlled trial of sclerotherapy vs ligation in the prophylactic treatment of high-risk esophageal varices. Surg Endosc. 1999;13(6):580–4.
8. Obara K. Treatment of esophagogastric varices. In: Endoscopic treatment of esophagogastric varices. Tokyo: Narunia Inc.; 2016. p. 21–46.
9. Masaki M, Mitsuhashi H, Kondo Y, et al. Studies on the mechanism of action of embolizing agent (ethanolamine oleate: EO) against esophageal varices: effect of endothelial injury. J Jpn Soc Gastroenterol. 1984;81:1491. [In Japanese].
10. Orikasa K, Masaki M, Sakamoto H, Mitsuhashi H, Wada T, Obara K, et al. In vitro assay for cytotoxicity of sclerosant against esophageal varices on human cultured endothelial cells. J Jpn Soc Gastroenterol. 1986;83:1409. [In Japanese with English abstract].
11. Orikasa K. Studies on the damage of the cultured endothelial cells and K-562 cells by sclerosants (ethanolamine oleate, Aethoxysklerol and absolute ethanol) used for treatment of esophageal varices. J Jpn Soc Gastroenterol. 1989;86:2365–72. [In Japanese with English abstract].
12. Masaki M, Obara K, Suzuki S, Orikasa K, Mitsuhashi H, Iwasaki K, et al. The destructive effects of sclerosant ethanolamine oleate on mammalian vessel endothelium. Gastroenterol Jpn. 1990;25(2):230–5. [In Japanese].
13. Obara K. EO/AS combination method. In: Toyonaga A, Makuuchi H, Obara K, editors. Esophagogastric varices. 2nd ed. Supervised by Suzuki H. Tokyo: Japan Medical Center; 2001. p. 145–5. [In Japanese].
14. Obara K, Sakamoto H, Kasukawa R. Action mechanisms of sclerosants and treatment outcomes: ethanolamine oleate. Clin Gastroenterol. 1991;6(1):79–88. [In Japanese].
15. Mima H, Yashiki T, Nakatani H, et al. Local use of nonionic water-soluble surfactant for injection. J Pharm Soc Jpn. 1962;82:1171–6. [In Japanese].

16. Kondo T. Mechanism of hemolysis by surface active agents. Adv Colloid Interf Sci. 1976;6:139–72.
17. Robertson JD. Unit membranes: a review with recent new studies of experimental alterations and a new subunit structure in synaptic membranes. In: Locke M, editor. Proc. 22nd Symp. Soc. Development and Growth, vol. 81. New York: Academic; 1964.
18. Fujiwara K. Study on endoscopic injection sclerotherapy for esophageal varices. Fukushima J Med. 1983;33:207–21. [In Japanese].
19. Mitsuhashi H. Basic study of endoscopic injection sclerotherapy: ulceration by EO, AS, and ET. In: Obara K, Saito Y, editors. Endoscopic injection sclerotherapy for esophageal varices. Supervised by Kasukawa R, Suzuki H. Osaka: Iyaku (Medicine and Drug) Journal Co., Ltd; 1991. p. 35–40. [In Japanese].
20. Sakamoto H. Basic study of endoscopic injection sclerotherapy: ethanolamine oleate (EO), Aaethoxysklerol (AS) and α-cyanoacrylate monomer (CA). In: Obara K, Saito Y, editors. Endoscopic injection sclerotherapy for esophageal varices. Supervised by Kasukawa R and Suzuki H. Osaka: Iyaku (Medicine and Drug) Journal Co., Ltd; 1991. p. 25–34. [In Japanese].
21. Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc. 2010;22(1):1–9. https://doi.org/10.1111/j.1443-1661.2009.00929.X.
22. The Japan Society for Portal Hypertension. The general rules for study of portal hypertension. 3rd ed. Tokyo: Kanehara & Co., Ltd; 2013. [In Japanese].
23. Obara K, Toyonaga A, Kokubu S. Guidelines for the endoscopic treatment of esophagogastric varices. In: Society for Japanese Gastroenterological Endoscopy, editor. Guidelines for gastrointestinal endoscopy. 3rd ed. Tokyo: Igaku-Shoin; 2006. p. 215–34. [In Japanese].
24. Kumagai Y, Makuuchi H, Tsuzuki T. Endoscopic classification of esophageal varices and its clinical significance. Stomach Intestine. 1976;11:741–50. [In Japanese].
25. Toyonaga A. Medical treatment of esophageal varices. In: Integrated handbook of internal medicine, vol. 86-A. Tokyo: Nakayama Shoten Co., Ltd; 1986. p. 143–70. [In Japanese].
26. Irisawa A, Obara K, Sakamoto H, Takiguchi F, Tojo A, Saito A, et al. The selection and evaluation of the manipulation for endoscopic injection sclerotherapy against esophageal varices with extra esophageal shunt. J PHEV. 1997;3:147–54. [In Japanese].
27. Sano A, Kuroda Y, Moriyasu F, Takahashi Y, Koizumi S, Kimura S, et al. Portopulmonary venous anastomosis in portal hypertension demonstrated by percutaneous transhepatic cineportography. Radiology. 1982;144:479–84.
28. Murakami M, Kokubu S, Yamagata S, Shirosaki K, Sugimoto M, Shibata H, et al. Study of complications with endoscopic varicealography during injection sclerotherapy in cases with portopulmonary venous anastomosis (PPVA). Gastroenterol Endosc. 1992;34:2543–51. [In Japanese with English abstract].
29. Sato T, Higashino K, Toyota J, et al. The usefulness of endoscopic color Doppler ultrasonography in the detection of perforating veins of esophageal varices. Dig Endosc. 1996;8:180–3.
30. Saito A, Obara K, Irisawa A, Takiguchi F, Tojo A, Ito M, et al. Experience of endoscopic injection sclerotherapy combined with selective endoscopic variceal ligation in 3 patients with esophageal varices accompanied by large extra-esophageal shunt. J PHEV. 1997;3:263–8. [In Japanese].
31. Obara K. Endoscopic injection sclerotherapy followed by mucosal fibrosis. JJPH. 2002;8:128–35. [In Japanese].
32. Deguchi H, Kato J, Maeda Y, Moribata K, Shingaki N, Niwa T, et al. Argon plasma coagulation is effective for prevention of recurrent esophageal varices after endoscopic injection sclerotherapy: single-center case-control study. Dig Endosc. 2016;28:42–9. https://doi.org/10.1111/den.12538.

Chapter 22
Endoscopic Treatment of Esophageal Varices: Kitano Method

Masayuki Ohta, Masafumi Inomata, and Seigo Kitano

Abstract A technique of endoscopic injection sclerotherapy (EIS) for esophageal varices, which Kitano et al. reported in 1987, consists of the use of an over-tube, a sclerosant of 5% ethanolamine oleate, and 1-week intervals between injections, with the EIS repeated until complete elimination of the lower esophageal mucosa. The technique was validated by several randomized controlled trials (RCTs) that were conducted by a portal hypertension group in the Department of Surgery II, Kyushu University. The results of 2105 cases showed that the cumulative nonbleeding rate was 90% at 15 years. This EIS technique was also compared with surgical procedures through another RCT and was equivalent to the surgical procedures in terms of nonbleeding and survival rates. In addition, the technique was also compared to endoscopic variceal ligation (EVL), and EVL significantly decreased the adverse effects associated with EIS. Although the EIS technique is now only performed in a limited number of institutions, it is safe, long-lasting, and established, and the achievement of favorable results remains excellent even now.

Keywords Esophageal varices · Endoscopic injection sclerotherapy · Eradication Ethanolamine oleate

22.1 Introduction

Crafoord et al. first reported endoscopic injection sclerotherapy (EIS) for esophageal varices in 1939 [1]. This technique was resurrected in the 1970s [2, 3], and since then, it has been widely performed throughout the world as the first choice of treatment for esophageal varices. Takase et al. introduced EIS to Japan in 1977 [4], but initially, the incidence of recurrent bleeding from the varices was relatively

M. Ohta (✉) · M. Inomata
Department of Gastroenterological and Pediatric Surgery,
Oita University Faculty of Medicine, Oita, Japan
e-mail: ohta@oita-u.ac.jp

S. Kitano
Oita University, Oita, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_22

high. Our initial experience in 50 patients with esophageal varices treated by EIS showed recurrent bleeding in over 20% of the patients [5]. Afterward, we developed a new technique that included the use of a transparent over-tube and elimination of the esophageal mucosa [6, 7]. The technique and its results are demonstrated here.

22.2 Technique of EIS (Kitano Method)

The technique of EIS, which Kitano et al. reported in 1987, is repeated at 1-week intervals using 5% ethanolamine oleate (EO) as the sclerosant to achieve elimination of the lower esophageal mucosa without X-ray fluoroscopy [7]. The initial session of EIS is performed using a transparent over-tube, a modified Williams sheath (K-S tube, ST-E1, Olympus Co., Ltd., Tokyo, Japan, discontinued in 2004, Fig. 22.1), which provides a clear field of vision and facilitates the precise injection of the sclerosant into the varices (Fig. 22.2a) [6, 8]. In the second session, the sclerosant is also injected into the varices using the over-tube or freehand technique. These two sessions of EIS attain thrombosis of the main variceal channels and of small venous channels that are located in the submucosa of the esophagus (Fig. 22.2b). In the third session, the sclerosant is injected not only into the thrombosed varices but also into the submucosa around the varices (Fig. 22.2c). Thereafter, further one or two sessions are performed to inject 5% EO into the residual esophageal submucosa (Fig. 22.2d), and then a superficial ulcer circumferentially forms in the lower 5–10 cm of the esophagus (Fig. 22.2e). At this time, the so-called complete eradication of the esophageal varices is achieved. A few weeks later, epithelialization of the surface of the ulcer becomes apparent and is replaced by fibrotic tissues, which prevent the recurrence of the esophageal varices, in the lower esophagus (Fig. 22.2f). A control endoscopy is performed every 3 months during follow-up, and an additional EIS treatment is added if small venous vessels appear in the lower esophagus.

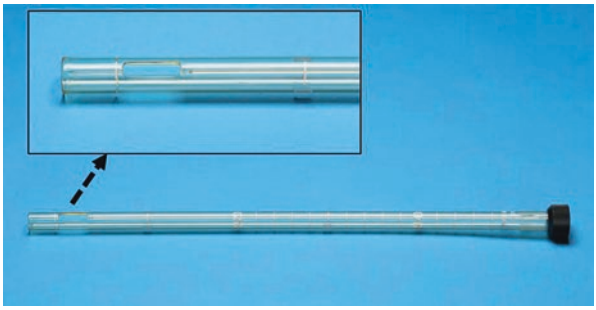


Fig. 22.1 The transparent over-tube (K-S tube, ST-E1, Olympus, Tokyo, Japan)

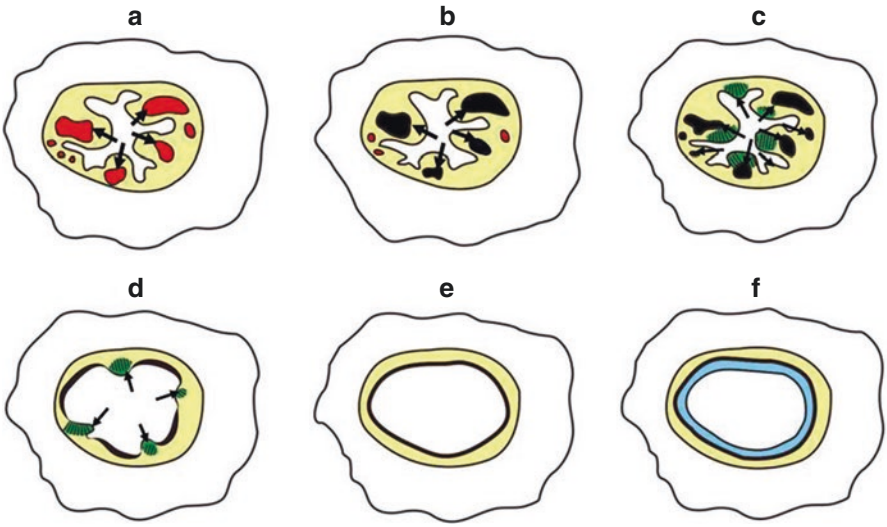


Fig. 22.2 Schemata of the technique of endoscopic injection sclerotherapy (EIS) reported by Kitano et al. in 1987 (Kitano method). (**a**, **b**) The initial and second sessions of EIS, respectively, with the precise injection of the sclerosant (5% ethanolamine oleate) into the varices. (**c**) The third session of EIS, with injection of the sclerosant into the thrombosed varices and submucosal tissues in the lower esophagus. (**d**) The fourth and/or fifth sessions of EIS, injection into the surrounding submucosa. (**e**) The superficial and circumferential ulcer in the lower esophagus after a sufficient number of EIS treatments. (**f**) Epithelialization of the surface of the ulcer and replacement of fibrotic tissues in the lower esophagus a few weeks after a sufficient number of EIS treatments

22.3 Results of EIS (Kitano Method)

Hashizume et al. reported the results in 1000 patients with esophageal varices [9], and Tomikawa et al. reported the results from 2105 cases, in Kyushu University [10]. Acute variceal bleeding was controlled in 99% of the 473 patients using the over-tube, and the early rebleeding rate was 4.5% [10]. Esophageal varices were completely eradicated in 84% of the 2105 patients with 3.8 ± 1.6 sessions of EIS (mean ± standard deviation). Treatment-related complications included esophageal stenosis, which required three or more sessions of endoscopic dilatation in 10% of the patients, esophageal variceal bleeding in 3.3%, esophageal ulcer bleeding in 1.2%, gastric variceal bleeding in 1.7%, gastritis bleeding in 1.6%, acute renal failure in 0.4%, and esophageal perforation in 0.1%. The cumulative recurrence rates of small venous vessels were 32% at 5 years, 37% at 10 years, and 38% at 15 years. The cumulative nonbleeding rates were 92% at 5 years, 90% at 10 years, and 90% at 15 years. The overall cumulative survival rate was 28% at 10 years.

Kitano et al. also compared their EIS technique to the surgical procedures of esophageal transection (ET) and distal splenorenal shunt (DSRS) in a prospective randomized trial (RCT) [11]. Ninety-six patients with esophageal varices and good liver function (Child class A or B) were randomly assigned to one of three groups. There was no mortality within 30 days in any of the groups. The cumulative non-bleeding rates at 5 years were not significantly different between the EIS group (100%), the ET group (94%), and the DSRS group (87%). In no case in the three groups did death occur because of variceal bleeding. The overall cumulative survival rates at 5 years were also not significantly different at 88% in the EIS, 74% in the ET, and 73% in the DSRS group. They concluded that EIS is a satisfactory alternative to ET or DSRS for the clinical management of patients with esophageal varices.

A typical case is presented here to show the treatment course of this technique. The patient was a 60-year-old man with risky esophageal varices (F2, Cw, RC3 [cherry red spot]) due to cryptogenic liver cirrhosis (Fig. 22.3a) [12]. The initial

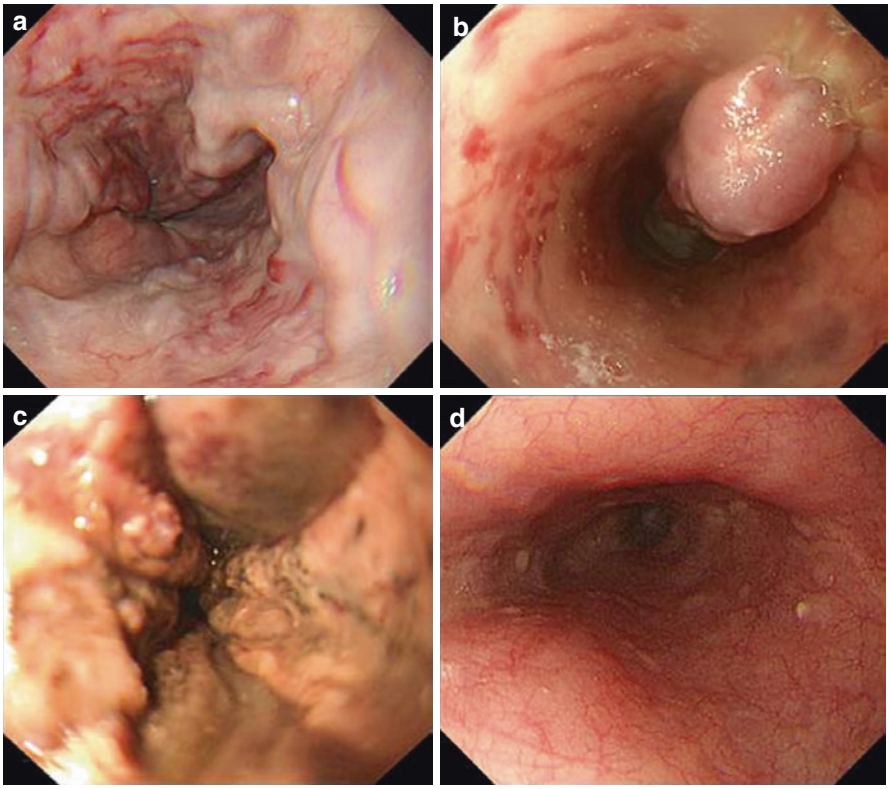


Fig. 22.3 Endoscopic findings of the lower esophagus in a patient with esophageal varices treated by the Kitano method. (**a**) Risky esophageal varices (F2, Cw, RC3) before treatment. (**b**) The initial session of endoscopic injection sclerotherapy (EIS) using the transparent over-tube. (**c**) Circumferentially necrotized mucosa in the lower esophagus after the four EIS sessions. (**d**) Current finding in the lower esophagus without recurrence of esophageal varices

session of EIS was prophylactically performed with the transparent over-tube (Fig. 22.3b). After four sessions of EIS (total volume of 5% EO, 44.5 mL), the lower esophageal mucosa was circumferentially necrotized (Fig. 22.3c). Afterward, the patient complained of esophageal stenosis, but endoscopic esophageal dilatation was not needed. He has remained alive without the recurrence of esophageal varices for 7 years (Fig. 22.3d).

22.4 Validation of the Technique

A portal hypertension group in the Department of Surgery II (Department of Surgery and Science), Kyushu University, conducted several RCTs to validate this EIS technique. They included comparisons between the over-tube and freehand techniques [8]; large and small volumes of 5% EO in the first session (30 mL vs. 15 mL) [13]; 5% EO and other sclerosants such as 1% polidocanol, 2% sodium tetradecyl sulfate, and 5% sodium morrhuate [14–16]; and sessions intervals of 1 and 2 weeks [17]. The over-tube technique was found to be significantly superior to the freehand technique in controlling variceal bleeding and rebleeding. A large volume of 5% EO administered in the initial session was also superior to a small volume with regard to postinjection bleeding and the number of subsequent sessions required. Compared to the other sclerosants, 5% EO was significantly better in terms of ulcer formation, esophageal stenosis, and postinjection bleeding. Regarding the intervals between sessions, treatment outcomes of the two interval methods were equivalent, but the 1-week interval method results in a significantly shorter hospital stay than the 2-week method. As a result, the EIS technique consisting of the use of an over-tube, a large volume of 5% EO sclerosant, and a 1-week interval of injection was validated.

22.5 Complications Due to 5% EO and Endoscopic Variceal Ligation

Complications due to 5% EO include acute renal failure, pulmonary edema and insufficiency, anaphylactic reaction, and disseminated intravascular coagulation. Renal failure due to 5% EO administration at the EIS sessions had been unknown, but Hashizume et al. first reported four cases [18]. They suspected that hemolysis due to the destruction of erythrocytes by 5% EO causes free hemoglobin and acute tubular necrosis in the kidney, and they demonstrated that haptoglobin can protect against renal damage from 5% EO. Miyoshi et al. also showed the protective effects of haptoglobin against 5% EO [19]. Injection of 5% EO into the superior vena cava in the canine models induced not only marked hemolysis and decreased creatinine clearance but also decreased blood flow to the renal artery [20]. Renal dysfunction due to 5% EO may be related to decreases in renal arterial blood flow. Albumin is known to be related to the inactivation of EO in the blood, and Ohta et al. first

demonstrated a relationship between albumin levels and hemolysis by EO [21]. They also analyzed clinical cases and showed that to prevent renal dysfunction, the serum albumin level may be corrected up to more than 3.0 g/dL before EIS. However, Kishihara et al. performed an experiment using analbuminemic rodent models and showed that serum albumin is related to the inactivation of EO, but other humoral substances may also be involved [22].

Endoscopic variceal ligation (EVL), which was developed by Stiegmann et al. [23], does not involve any complications due to sclerosants. EVL has lower rates of rebleeding, mortality, and complications than EIS [24] and continues to be widely performed throughout the world. Hashizume et al. performed a RCT to compare EVL to EIS (Kitano method) in the initial session and showed that EVL significantly decreases adverse effects such as the chest pain, pleural effusion, and renal dysfunction associated with EIS and is recommended as an alternative to EIS [25]. They followed the subjects of this RCT for 3 years and showed a significant difference in the cumulative recurrence rates of small venous vessels at 3 years between the EVL + EIS group (90%) and the EIS group (35%) [26]. Therefore, EVL is thought to be safer than EIS but needs close follow-up by endoscopy to prevent the recurrence of and rebleeding from esophageal varices.

22.6 Conclusion

EIS using the Takase method or the Obara method is generally performed in Japan, but EIS using the Kitano method introduced in this chapter is now only performed in a limited number of institutions. We do not know the reason why EIS using the Kitano method did not become a major technique in Japan. However, this technique is safe, long-lasting, and established, and continues to achieve favorable results remains even now.

References

1. Crafoord C, Frenckner P. New surgical treatment of varicose veins of the oesophagus. Acta Otolaryngol. 1939;27:422–9.
2. Johmston GW, Rodgers HW. A review of 15 years' experience in the use of sclerotherapy in the controls of acute haemorrhage from oesophageal varices. Br J Surg. 1973;33:797–800.
3. Terblanche J, Northover JM, Bornman P, Kahn D, Silber W, Barbezat GO, et al. A prospective controlled trial of sclerotherapy in the long term management of patients after esophageal variceal bleeding. Surg Gynecol Obstet. 1979;148:323–33.
4. Takase Y, Ozaki A, Oril K, Nagoshi K, Okamura T, Iwasaki Y. Injection sclerotherapy of esophageal varices for patients undergoing emergency and elective surgery. Surgery. 1982;92:474–9.
5. Kitano S, Hashizume M, Yamaga H, Wada H, Sugimachi K. Endoscopic injection sclerotherapy: variants of sclerotherapy technique. J Gastroenterol Hepatol. 1989;4(Suppl 1):171–2.

6. Kitano S, Sugimachi K. A rapid and relatively safer method of sclerosing esophageal varices utilizing a new transparent tube. Am J Surg. 1987;153:317–9.
7. Kitano S, Koyanagi N, Iso Y, Higashi H, Sugimachi K. Prevention of recurrence of esophageal varices after endoscopic injection sclerotherapy with ethanolamine oleate. Hepatology. 1987;7:810–5.
8. Kitano S, Koyanagi N, Iso Y, Iwanaga T, Higashi H, Sugimachi K. Prospective randomized trial comparing two injection techniques for sclerosing oesophageal varices: over-tube and free-hand. Br J Surg. 1987;74:603–6.
9. Hashizume M, Kitano S, Koyanagi N, Tanoue K, Ohta M, Wada H, et al. Endoscopic injection sclerotherapy for 1,000 patients with esophageal varices: a nine-year prospective study. Hepatology. 1992;15:69–75.
10. Tomikawa M, Hashizume M, Okita K, Kitano S, Ohta M, Higashi H, et al. Endoscopic injection sclerotherapy in the management of 2105 patients with esophageal varices. Surgery. 2002;131(Suppl 1):S171–5.
11. Kitano S, Iso Y, Hashizume M, Yamaga H, Koyanagi N, Wada H, et al. Sclerotherapy vs. esophageal transection vs, distal splenorenal shunt for the clinical management of esophageal varices in patients with Child class A and B liver function: a prospective randomized trial. Hepatology. 1992;15:63–8.
12. Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc. 2010;22:1–9. https://doi.org/10.1111/j.1443-1661.
13. Iso Y, Kitano S, Iwanaga T, Koyanagi N, Sugimachi K. A prospective randomized study comparing the effects of large and small volumes of the sclerosant 5% ethanolamine oleate injected into esophageal varices. Endoscopy. 1988;20:285–8.
14. Kitano S, Iso Y, Koyanagi N, Higashi H, Sugimachi K. Ethanolamine oleate is superior to polidocanol (aethoxysklerol) for endoscopic injection sclerotherapy of esophageal varices: a prospective randomized trial. Hepatogastroenterology. 1987;34:19–23.
15. Kitano S, Iso Y, Yamaga H, Hashizume M, Higashi H, Sugimachi K. Trial of sclerosing agents in patients with oesophageal varices. Br J Surg. 1988;75:751–3.
16. Kitano S, Wada H, Yamaga H, Hashizume M, Koyanagi N, Iwanaga T, et al. Comparative effects of 5% ethanolamine oleate versus 5% sodium morrhuate for sclerotherapy of oesophageal varices. J Gastroenterol Hepatol. 1991;6:476–80.
17. Higashi H, Kitano S, Hashizume M, Yamaga H, Sugimachi K. A prospective randomized trial of schedules for sclerosing esophageal varices. 1- versus 2-week intervals. Hepatogastroenterology. 1989;36:337–40.
18. Hashizume M, Kitano S, Yamaga H, Sugimachi K. Haptoglobin protect against renal damage from ethanolamine oleate sclerosant. Lancet. 1988;2:340–1.
19. Miyoshi H, Ohshiba S, Matsumoto A, Takada K, Umegaki E, Hirata I. Haptoglobin prevents renal dysfunction associated with intravariceal infusion of ethanolamine oleate. Am J Gastroenterol. 1991;86:1638–41.
20. Wada H, Hashizume M, Yamaga H, Kitano S, Sugimachi K. Hemodynamic and morphological changes in the dog kidney after injection of 5% ethanolamine oleate into the superior vena cava. Eur Surg Res. 1990;22:63–70.
21. Ohta M, Hashizume M, Ueno K, Tanoue K, Sugimachi K. Albumin inhibits hemolysis of erythrocytes induced by ethanolamine oleate during endoscopic injection sclerotherapy. Hepatogastroenterology. 1993;40:65–8.
22. Kishihara F, Ohta M, Hashizume M, Tomikawa M, Kawanaka H, Tanoue K, et al. Systemic effects of ethanolamine oleate in analbuminemic rats. Hepatogastroenterology. 1999;46:376–80.
23. Stiegmann VG, Goff JS. Endoscopic esophageal varix ligation: preliminary clinical experience. Gastrointest Endosc. 1988;34:113–7.

24. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Intern Med. 1995;123:280–7.
25. Hashizume M, Ohta M, Ueno K, Tanoue K, Kitano S, Sugimachi K. Endoscopic ligation of esophageal varices compared with injection sclerotherapy: a prospective randomized trial. Gastrointest Endosc. 1993;39:123–6.
26. Hashizume M, Ohta M, Kawanaka H, Kishihara F, Sugimachi K. Recurrence rate of oesophageal varices with endoscopic banding ligation followed by injection sclerotherapy. Lancet. 1994;344:1643.

Chapter 23
Endoscopic Treatment of Esophageal Varices: Takase Method

Fumio Chikamori and Yasuhiro Takase

Abstract Endoscopic injection sclerotherapy (EIS), using the Takase method is now widely accepted and used to treat esophageal varices.

Intravariceal injection of 5% ethanolamine oleate with contrast iopamidol embolizes the varices along with blood supply routes. Portal hemodynamics and liver function are not affected after EIS. The recurrence rates of esophageal varices at 2 years after EIS with complete and incomplete embolization of blood supply routes were 7% and 70%, respectively ($p < 0.05$). Because of this result, we consider the complete embolization of varices and their blood supply routes with EIS to be the first-choice treatment for esophageal varices to diminish the variceal recurrence rate.

Keywords Endoscopic injection sclerotherapy · Esophagogastric varices · Blood supply route · 5% Ethanolamine oleate with iopamidol

23.1 Introduction

Clafoord and Frenckner [1] reported the first experience with endoscopic injection sclerotherapy (EIS) using rigid scope in 1939. Takase et al. [2] first treated a patient with esophageal varices by EIS using a fiberscope in 1977. EIS is now widely accepted and used to treat esophageal varices. It can be performed either by treating esophageal varices in isolation [3–5] or treating esophageal varices along with their blood supply routes using the Takase method [2, 6, 7].

It has been considered that esophageal transection with devascularization of the proximal half of the stomach is a rational operation for esophagogastric varices, and the recurrence rate treated with it is lower than that treated with esophageal transection without devascularization [8–10]. Even with minimally invasive endoscopic treatment, we recommend that esophageal varices should be treated together with

F. Chikamori (✉)
Department of Surgery, Tano Hospital, Kochi, Japan

Y. Takase
Department of Surgery, Tsukuba Soai Hospital, Tsukuba, Ibaraki, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_23

blood supply routes such as the cardiac branch of the left gastric vein (LGV) or the cardiac venous plexus (CP), which often forms cardiac varices. Intravariceal injection of 5% ethanolamine oleate with contrast iopamidol (5% EOI) embolizes the varices along with blood supply routes [2, 6, 7].

23.2 Technical Aspects

Patients with esophageal varices are intramuscularly injected with pentazocine 15 mg and hydroxyzine hydrochloride 25 mg 30 min before the procedure as premedication. A balloon made of Teflon is attached to the distal end of endoscope. After careful endoscopic visualization of the esophageal varices, the attached balloon is filled with 15–20 ml of air to prevent the blood and embolizing medicine from flowing into the azygos vein. The medicine mixed with contrast media is injected intravariceally under fluoroscopy [2, 6, 7]. The flow of the sclerosant is monitored by endoscopic varicography, and the injection is stopped when the blood supply routes of the varices are filled with sclerosant or the paraesophageal, inferior phrenic, or mediastinal drainage veins are observed.

23.3 Effects of Takase Method on Portal Hemodynamics

Five percent EOI is an endothelial irritant and activates the coagulation in vivo. It damages the endothelium when injected intravenously and produces sterile dose-related inflammatory response resulting in fibrosis and occlusion of the vein. Excessive amount of 5% EOI flowing into the portal vein could potentially lead to portal vein thrombosis.

We investigated the short-term effects of EIS using the Takase method on portal hemodynamics in patients with esophageal varices and cirrhosis using a duplex Doppler flowmeter [11]. No significant change was observed in portal venous flow or liver function after EIS. Comparing pre- and post-percutaneous transhepatic variceal obliteration (PTO), Ohnishi et al. [12] reported a significant increase in portal blood flow observed after PTO. The hemodynamic changes caused by EIS are not similar to those seen after PTO. While PTO or esophageal transection with devascularization for esophageal varices means complete disconnection of the gastroazygous venous system, EIS using the Takase method results in disconnection of the esophagogastric varices and their blood supply routes. It may be possible to develop the extraesophageal connection of the portoazygous venous system after EIS to absorb portal pressure and possibly minimize variceal recurrence.

23.4 Recurrence of Esophageal Varices After EIS

We evaluated the degree of obliteration of the varices and their blood supply routes by percutaneous transhepatic portography (PTP) performed 1–2 weeks before and after EIS [13]. Using the transhepatic approach, a 5-French catheter was inserted into the splenic and left gastric veins, and 24 and 21 ml of contrast medium were injected at the rate of 4 and 3 ml/s, respectively. The recurrence rates of esophageal varices at 2 years after EIS with complete and incomplete embolization of supply routes were 7% and 70%, respectively ($p < 0.05$) [13]. Because of this result, we consider that complete embolization of varices and their blood supply routes with EIS is the first-choice treatment for esophageal varices to diminish the variceal recurrence rate.

23.5 Case Report

A 65-year-old man presents with esophageal varices resulting from cirrhosis. The PTP prior to the EIS showed that the anterior branch of the LGV had formed the CP which drained to the esophageal varices (Fig. 23.1a). Using the Takase method, the sclerosant was injected not only into the esophageal varices but also into the anterior branch of the LGV through CP (Fig. 23.1b). PTP after the EIS demonstrated the thrombosis of the varices, the CP, and the anterior branch of the LGV. Posterior branch of LGV, which had formed a gastrorenal shunt, was not affected (Fig. 23.1c).

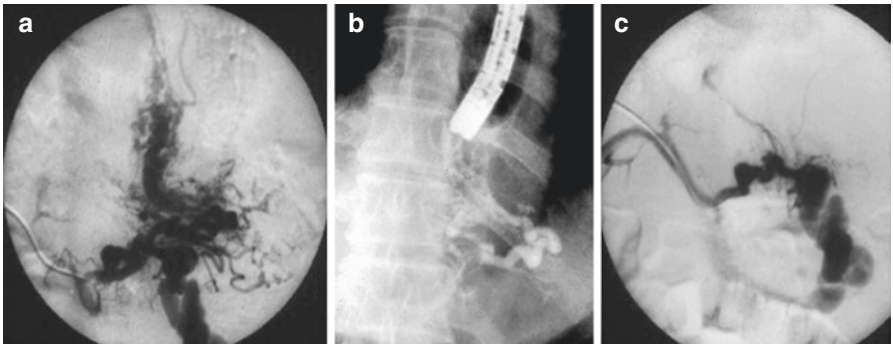


Fig. 23.1 (**a**) The PTP prior to the EIS showing that the anterior branch of the LGV forms the CP which drains to the esophageal varices. (**b**) Endoscopic varicogram showing that the sclerosant is injected into the anterior branch of the LGV through the CP. (**c**) The PTP after the EIS showing that the posterior branch of the LGV forms a gastrorenal shunt

23.6 Conclusions

We conclude that complete embolization of varices and their blood supply routes with EIS is the first-choice treatment for esophageal varices to diminish the variceal recurrence rate.

Acknowledgments I thank Dr. Niranjan Sharma PhD, Mornington Health Center, Dunedin, New Zealand, for helpful comments.

References

1. Clafoord C, Frenckner P. New surgical treatment of varicose veins of the oesophagus. Acta Otolaryngol. 1939;27:422–9.
2. Takase Y, Ozaki A, Orii K, Nagoshi K, Okamura T, Iwasaki Y. Injection sclerotherapy of esophageal varices for patients undergoing emergency and elective surgery. Surgery. 1982;92:474–9.
3. Terblanche J, Yakoob H, Bornman PC, Stiegmann GV, Bane R, Jonker M, et al. Acute bleeding varices. A five-year prospective evaluation of tamponade and sclerotherapy. Ann Surg. 1981;194:521–9.
4. Soehendra N, Heer K, Kempeneers I, Runge M. Sclerotherapy of esophageal varices: acute arrest of gastrointestinal hemorrhage or long-term therapy. Endoscopy. 1983;15:136–40.
5. Stiegmann GV, Goff JS, Michaletz-Onody PA, Korula J, Lieberman D, Saeed ZA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med. 1992;326:1527–32.
6. Takase Y, Shibuya S, Sharma N. Radiological control of injected sclerosant for esophageal varices by endoscopic varicography during injection sclerotherapy. Dis Esophagus. 1990;3:23–32.
7. Chikamori F, Aoyagi H, Takagaki T, Sharma N, Shibuya S, Takase Y. Injection sclerotherapy for esophageal varices after total gastrectomy: case report of two patients. Dig Endosc. 1992;4:274–80.
8. Idezuki Y, Sanjo K. Twenty-five-year experiences with esophageal transection for esophageal varices. J Thorac Cardiovasc Surg. 1989;98:876–83.
9. Sugiura M, Futagawa S. Esophageal transection with paraesophagogastric devascularizations (the Sugiura procedure) in the treatment of esophageal varices. World J Surg. 1984;8:673–82.
10. Walker RM. Transection operation for portal hypertension. Thorax. 1960;15:218–24.
11. Chikamori F, Kuniyoshi N, Shibuya S, Takase Y. Short-term portal hemodynamic effects of endoscopic embolization for esophageal varices. Dig Surg. 2000;17:454–8.
12. Ohnishi K, Nakata H, Terabayashi H, Tanaka H, Tsunoda T, Iida S, Nomura F. The effect of endoscopic sclerotherapy combined with transhepatic variceal obliteration on portal hemodynamics. Am J Gastroenterol. 1987;82:1138–42.
13. Takase Y, Shibuya S, Chikamori F, Orii K, Iwasaki Y. Recurrence factors studied by percutaneous transhepatic portography before and after endoscopic sclerotherapy for esophageal varices. Hepatology. 1990;11:348–52.

Chapter 24
Endoscopic Treatment of Esophageal Varices: Suzuki Method

Hiroaki Suzuki and Manabu Yamamoto

Abstract The Suzuki method was established in 1979 and is a unique intra- and para-variceal combined injection technique using 1% polidocanol (Aethoxysclerol).

From 1979 to 1987, we performed this procedures a total 878 times on 276 patients. There were 94 emergency, 92 elective, and 90 prophylactic cases.

We use Aethoxysclerol as the safest sclerosant since it has low toxicity and low viscosity. The injections are first made into a submucosal site between the varices and then into each variceal channel, using 3 mL in each injection. The total dose of sclerosant is limited to 30 mL per one session of therapy. We perform the endoscopic injection sclerotherapy (EIS) by freehand technique without any sheath or balloon, using a flexible 23 or 25 gauge fine needle under intravenous sedation and topical anesthesia. As a rule, three sessions of EIS are performed at weekly intervals, and a follow-up study is done every 3 months for choosing additional therapy or observation.

As a result, the hemostatic rate was as high as 91% and the eradicating rate was 92%.

The Suzuki method is an effective treatment for both acute variceal bleeding and bleeding prophylaxis.

Keywords EIS · Esophageal varices · Endoscopic sclerotherapy · Aethoxysclerol · Polidocanol

24.1 Introduction

Endoscopic injection sclerotherapy (EIS) is now a standard and a first-line treatment for esophageal varices. The Suzuki method was established in 1979 and is a unique intra- and para-variceal combined injection technique with 1% polidocanol.

H. Suzuki
Department of Endoscopy, Jikei University School of Medicine, Tokyo, Japan

M. Yamamoto (✉)
Adachi Kyosai Hospital, Tokyo, Japan
e-mail: fm3m-ymmt@asahi-net.or.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_24

Since then, the Suzuki method has been widely accepted and used as a safe and effective treatment method and is still being employed with many improvements.

In this paper, the background to the Suzuki method is introduced with a focus on the historical aspects of its originality.

24.2 Backgrounds

According to the results of emergency surgery for upper GI bleeding in our institution (1949–1980), the mortality rate was very high (27.8%) in esophageal varices patients compared with peptic ulcer (3.4%) or gastric cancer patients (11.1%).

Therefore, we introduced EIS in order to avoid emergency surgery for bleeding esophageal varices in March 1979.

EIS has gained increasing acceptance in the control of variceal bleeding. In this paper, the technique we used and the results of EIS in patients with esophageal varices observed over an 8-year period (1979–1987) are described.

24.3 Materials and Methods

From 1979 to 1987, we practiced EIS not only to control acute variceal bleeding but also to prevent possible rebleeding by eradication of varices. We performed 878 EIS sessions in total on 276 patients. There were 94 emergency, 92 elective, and 90 prophylactic cases.

The constitution of cases according to Child's classification was 166 cases in Child A or B, and 110 in Child C, with the majority of them not being candidates for surgery (Table 24.1).

Emergency EIS consisted of volume resuscitation according to the Nagao's gradation [1] of bleeding followed by endoscopy. The nature and source of bleeding were defined with emergency endoscopy and treated by EIS at one time in most of the cases.

Figure 24.1 illustrates our ordinary injection technique and typical course of variceal eradication after the therapy. We use 1% polidocanol (Aethoxysclerol) as the safest sclerosant. It has very low toxicity and in addition its viscosity is low.

Table 24.1 Constitution of cases according to the timing of therapy and the Child's classification

Timing of therapy	No. of cases	Child's classification	No. of cases
Emergent	94	A	37
Elective	92	B	129
Prophylactic	90	C	110
Total	276		276

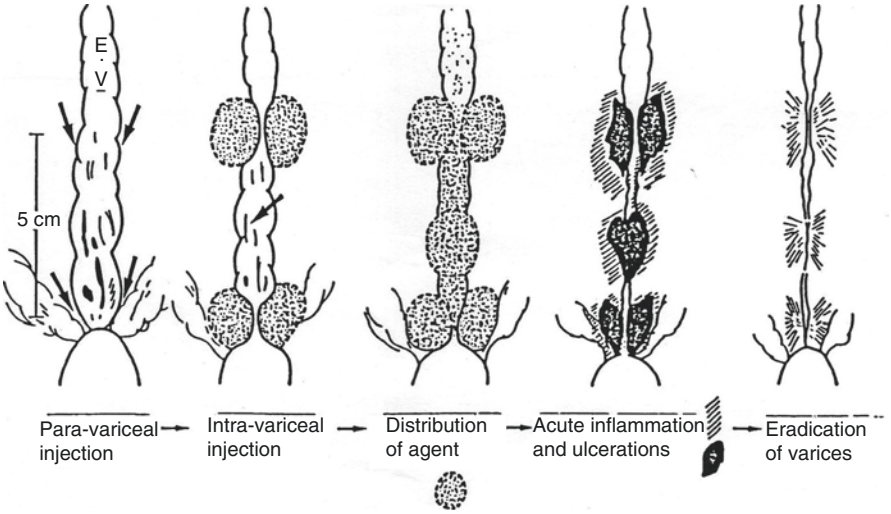


Fig. 24.1 Injection techniques and typical course to eradication of varices after therapy

The injections are first made into a submucosal site between the varices and then into each variceal channel, using 3 mL in each injection. This combined injection technique was first reported by the authors in 1980 [1]. Total dose of sclerosant is limited to 30 mL per session of therapy. We perform EIS by freehand technique without any sheath or balloon, using a flexible 23- or 25-gauge fine needle under intravenous sedation and topical anesthesia.

All patients received a standard ulcer therapy with either H_2 blockers or PPI after the EIS. Peroral feeding is permitted from the next day and gradually upgraded from liquid meal to soft meal.

Typically, 1 or 2 weeks after the EIS, ulcerations occur on and around the varices, and finally, varices are remarkably diminished or disappeared due to the fibrotic change by healing ulcers.

As a rule, three sessions of EIS are performed once every week, and a follow-up study is done every 3 months for choosing additional therapy or observation.

24.4 Results

24.4.1 Hemostatic Effects on Emergency Variceal Bleeding

The hemostatic effect of our EIS series was studied in 94 emergency cases [2]. There were 57 cases with active bleeding at the emergency endoscopy. Bleeding was stopped by EIS for more than 72 h in 52 cases, and the hemostatic rate was as high as 91%. Even in 33 cases out of 57 with severe blood spurting, a high hemostatic rate of 88% was obtained.

Table 24.2 Hemostatic effects in emergency variceal bleeding

At emergency endoscopy ($n = 94$)	Endoscopic findings (No. of cases)	Hemostatic effects (No. of cases (%))	
Active bleeding ($n = 57$)	Blood spurting (33)	29 (88)	52 (91)
	Blood oozing (24)	23	
Non-active bleeding ($n = 37$)	Red emboli		
	Fibrin emboli		

Other than these patients, there were 37 cases of red or fibrin emboli without active bleeding at the time of endoscopy. In all these cases, bleeding was also controlled by EIS (Table 24.2). Hemostasis was not achieved in five cases, which were treated by other therapies such as SB tube and medical treatments and so forth, but no surgeries were required.

24.4.2 Eradicating Effects on Varices

We also evaluated the eradicating effects on varices after the EIS. We consider that the merits of EIS are not only its hemostatic effect but also its eradicating effect on varices which leads to prophylaxis of possible bleeding.

One hundred and thirty-nine cases followed up for more than 3 months after the EIS were studied at that time.

The forms, namely, F number of varices classified by the Japanese Society of Portal Hypertension [3], are shown in Fig. 24.2. Lines declining to the right side show the improvement of variceal forms, i.e., an eradicating effect. In total, the eradicating effects were obtained in 128 out of 139 cases with an efficacy rate of 92%. The right column shows the rebleeding rate according to postoperative F number. It is worth noting that in successful EIS with reduction in F number to F1 or less, there is extremely little risk of rebleeding.

24.4.3 Long-Term Survival

The long-term survival curve studied by the Kaplan-Meier method from the viewpoint of timing of therapy is shown in Fig. 24.3.

Survival for more than 5 years was obtained in 77% of elective or prophylactic cases while only 33% of emergency cases survived.

Furthermore, the results of long-term survivals of the emergency cases were studied from the viewpoint of the Child's classification (Fig. 24.4). Child A group could survive in all cases, and Child B group had 68% survival rate for more than

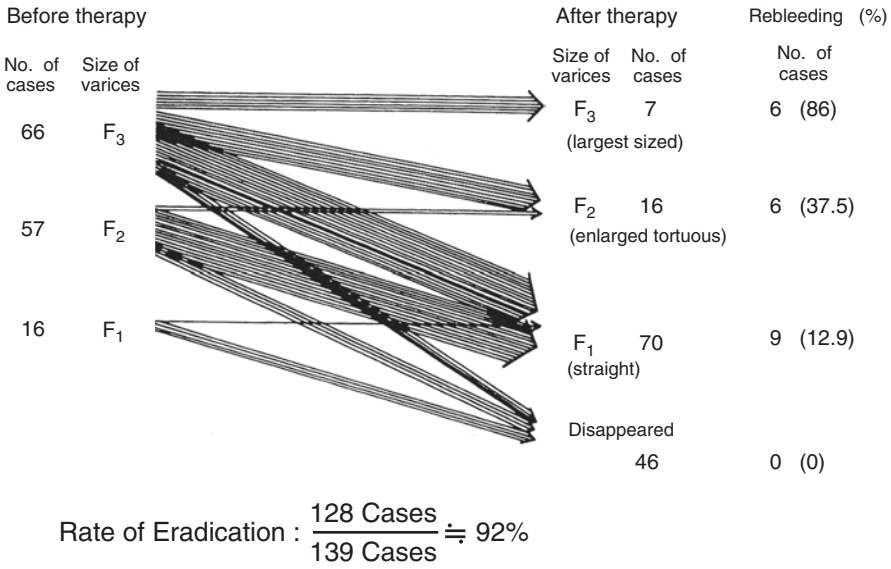


Fig. 24.2 Eradicating effects on varices and prevention of rebleeding

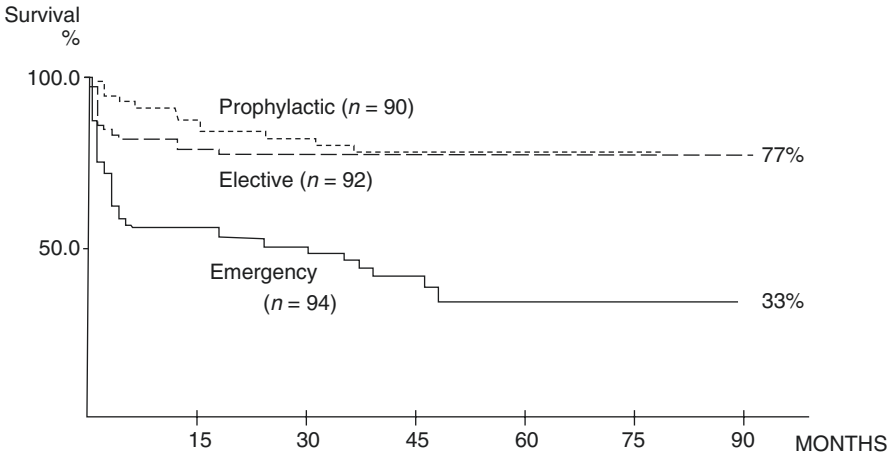


Fig. 24.3 Long-term survival curve

5 years even in emergency cases. On the other hand, only 18% of the Child C group patients survived in emergency cases.

In other words, the prognosis of the patients treated by EIS is influenced by the timing of therapy and the Child score.

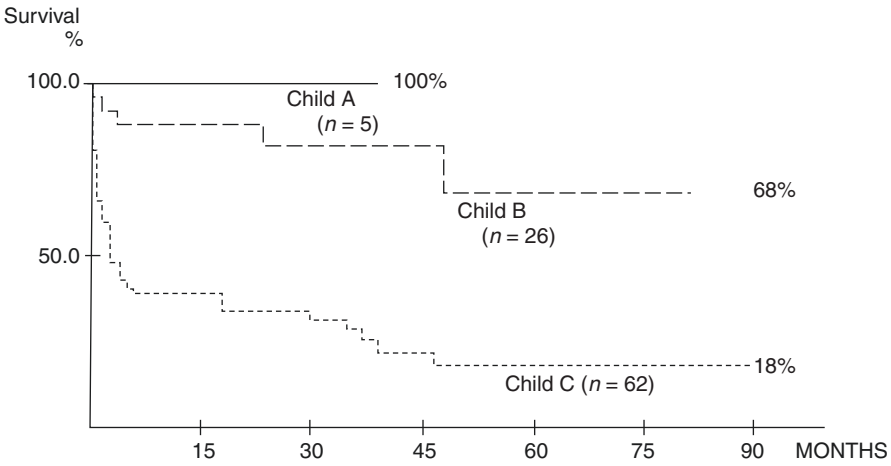


Fig. 24.4 Long-term survival in emergency cases

24.5 Discussion

In recent years, EIS has been widely accepted in the control of acute variceal bleeding and eradicating varices.

EIS is a palliative treatment for esophageal varices because it cannot improve the background disease of the liver. However, by eliminating recurrent bleeding, the survival rate can be increased. Furthermore, we consider that the purpose of EIS for esophageal varices is not only to control acute bleeding but also to prevent potential bleeding by eradication of varices.

Many controversies are still existing concerning EIS on the timing of therapy or the technique. Westaby [4] reported an appropriate timing to be within 12 h of the initial control of bleeding by balloon tamponade.

Terblanche [5] notes optimal timing to be in the bleeding-free interval under general anesthesia at a convenient time in daylight hours, and he also selects balloon tamponade for the initial control of active variceal bleeding.

Figure 24.5 shows our contingency plan to control acute bleeding from esophageal varices. Commonly in the daytime, we select the EIS as the first-choice procedure to control the bleeding, but at the weekend or at night, balloon tamponade should be selected because of its simplicity and certainty for operation. We perform EIS as a continuation of the emergency endoscopy under intravenous sedation without general anesthesia.

In our study, 57 active bleeders (33 blood spurting and 24 oozing) were found by emergency endoscopy in 94 cases. Even in such serious bleeding cases, 91% could be controlled. If the bleeding point can be detected at the emergency endoscopy, we consider the efficacy of subsequent EIS on liberation from the distress accompanied by the balloon tamponade.

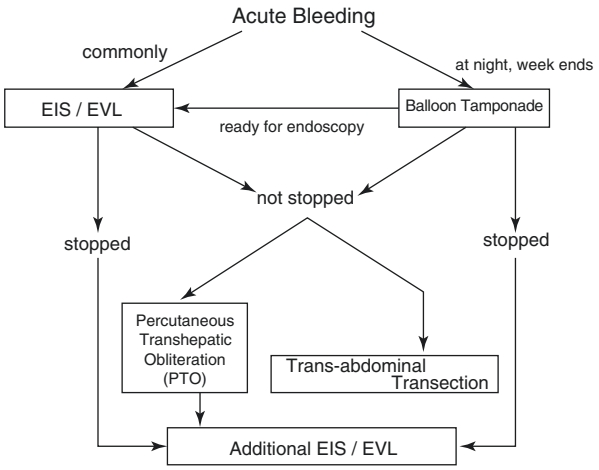


Fig. 24.5 Contingency plan to control acute bleeding from esophageal varices

With regard to injection technique, the King's College group employs an esophageal sheath (Williams tube) [6] as the injection apparatus and 5% ethanolamine oleate as the sclerosant. Takase et al. [7] also select 5% ethanolamine oleate with contrast medium to embolize the varices using a balloon-attached fiberscope.

Our injection technique with 1% polidocanol, the so-called para- and intravariceal combined injection technique (Suzuki method), is simpler without using either balloon or sheath [7].

As the next steps of the Suzuki method, we introduced endoscopic variceal ligation (EVL) [8, 9] in order to improve the hemostatic effect and eradication effect of esophageal varices with the help of G. Stiegmann (Colorado, USA) and co-author M. Yamamoto in 1988. Also in 1988, we introduced the Histoacryl injection technique [10] to control acute bleeding from gastric varices with the help of N. Soehendra (Hamburg, Germany). The abovementioned endoscopic therapies were very helpful in avoiding emergency surgery by achieving complete control of the bleeding from esophageal and gastric varices. In the twenty-first century, endoscopic treatments are recognized as the most reliable and least invasive technique for the control of variceal bleeding.

24.6 Conclusions

EIS is the important treatment technique both for acute variceal bleeding and for the prevention of initial or recurrent variceal bleeding. According to the recent trends, emergency surgery for the variceal bleeding is almost eliminated. In conclusion, we consider that the simplification of the technique is one of the most important points for popularizing the EIS, and the additional EIS to eradicate the varices is also the important point for prophylaxis of rebleeding.

References

1. Nagao F, Suzuki H. Drug therapy for gastrointestinal bleeding (in Japanese). Surg Diagn Treat. 1980;22:1127–32.
2. Suzuki H, Kohyama M, Nagata T, Watanabe Y, Nagao F. Endoscopic sclerotherapy for the control of bleeding from esophageal varices. In: Okabe H, Honda T, Ohshiba S, editors. Endoscopic surgery. Amsterdam: Excerpta Medica; 1984. p. 23–30.
3. The Japan society for portal Hypertension. The general rules for study of portal hypertension (in Japanese). 3rd ed. Tokyo: Kanehara & Co., Ltd; 2013.
4. Westaby D, Williams R. Injection sclerotherapy for the long-term management of variceal bleeding. World J Surg. 1984;8:667–72.
5. Terblanche J, Bornman PC, Kahn D, Kirsh RE. Sclerotherapy in acute variceal bleeding: technique and results. Endoscopy. 1986;18:23–7.
6. Williams KGD, Dawson JL. Fibreoptic injection of oesophageal varices. Br Med J. 1979;2:766–7.
7. Takase Y, Ozaki A, Orii K, et al. Injection sclerotherapy of esophageal varices for patients undergoing emergency and selective surgery. Surgery. 1982;92:474–6.
8. Stiegmann GV. Fifteen years of endoscopic variceal ligation for bleeding esophago- gastric varices. Endoscopia Digestiva. 2001;13:1253–61.
9. Suzuki H. Endoscopic variceal ligation. Asian Med J. 1988;42:362–6.
10. Suzuki H, Yamamoto M, Chibai M. Endoscopic injection sclerotherapy for gastric varices. Prog Dig Endosc. 1988;33:83–6.

Chapter 25
Endoscopic Treatment of Esophageal Varices: Consolidation Method Following Ethanolamine Oleate-Aethoxysklerol Combination Therapy

Katsutoshi Obara

Abstract To further reduce the rate of recurrence following the eradication of esophageal varices with endoscopic injection sclerotherapy using ethanolamine oleate (EO)-aethoxysklerol (AS) combination method, we introduced the consolidation method (mucosal fibrosis method using AS, laser, or argon plasma coagulation (APC)). The consolidation method for esophageal varices consists essentially of complete disappearance of esophageal varices using the EO-AS combination method followed by fibrosing of the lower esophagus with AS, laser, or APC. APC consolidation has been widely performed to date due to its usability and efficacy in further preventing variceal recurrence. Although the whole lower esophagus is treated including thrombotic varices and normal esophageal mucosa, this method can make fibrosis all round in the esophageal wall without esophageal stenosis. APC has also been used to prevent recurrence after endoscopic variceal ligation and is reported to be effective.

Keywords Esophageal varices · Obara method (EO-AS combination method) APC consolidation method (mucosal fibrosis method using APC) · EVL-AS combination method and APC consolidation method

25.1 Introduction

In Japan, endoscopic injection sclerotherapy (EIS) in the form of the ethanolamine oleate (EO)-aethoxysklerol (AS) combination method (Obara method) was introduced by Obara et al. in 1987 [1] and has been widely performed as an effective therapy for the eradication and recurrence prevention of esophageal varices. However, although the EO-AS combination method has led to a reduction in the

K. Obara
Department of Advanced Gastrointestinal Endoscopy, Fukushima Medical University, Fukushima, Fukushima, Japan
e-mail: k-obara@fmu.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_25

recurrence rate, a non-bleeding recurrence rate of 31.3% was reported 5 years after the complete eradication of esophageal varices. Nevertheless, among those cases treated using the EO-AS combination method, esophageal stricture was observed as a complication of AS injection in some cases where no recurrence had been found even 5 or 6 years after treatment, which suggested that recurrence might be prevented if recurrence-prone veins were thoroughly treated with AS.

In 1989, Obara et al. [2] introduced the AS consolidation method (mucosal fibrosis method using AS); however, of 42 cases treated using this method, 10 (23.8%) were associated with esophageal stricture, which required endoscopic balloon dilatation. Accordingly, in 1994, Obara et al. introduced the laser consolidation method (the mucosal fibrosis method using a laser) [3], under which the lower esophageal mucosa is irradiated with a laser circumferentially to form a circumferential ulcer and replace the breeding bed for esophageal varices with a mass of dense fibrous tissues without causing esophageal stricture. In 1994, Grund KE et al. [4] reported the first clinical experience of endoscopic argon plasma coagulation (APC) to upper and lower gastrointestinal tracts using special application probes developed by the authors, which fit into the working channel of standard endoscopes. Following this, APC consolidation (mucosal fibrosis using APC) began to be applied to obliterated esophageal varices and has been widely applied to date on account of its efficacy and ease of application.

This chapter describes the indications, procedures, and efficacy of the APC consolidation method.

25.2 APC Consolidation Therapy

25.2.1 Indications

Treatment with the APC consolidation method is indicated for bleeding cases, elective cases, and recurrent cases. For prophylactic cases, this method is indicated for endoscopic treatment-resistant cases, alcohol-related cirrhosis cases, and hepatocellular carcinoma-complicated cases with portal vein invasion (Vp) 0-2 [5, 6]. Moreover, the APC consolidation method is indicated for cases where the advanced development of periesophageal veins and the presence of large perforating veins are observed with an ultrasound miniprobe after the completion of EIS because such cases display a high potential for recurrence [7].

25.2.2 APC Consolidation Procedure Following the EO-AS Combination Therapy

In open surgery, laparoscopic surgery, and thoracoscopic surgery, APC has been used for the hemostasis of superficial and diffuse hemorrhages from parenchymatous organs and for the devitalization of various tissues. Moreover, in endoscopic treatment, the development of special probes, which can be applied through flexible

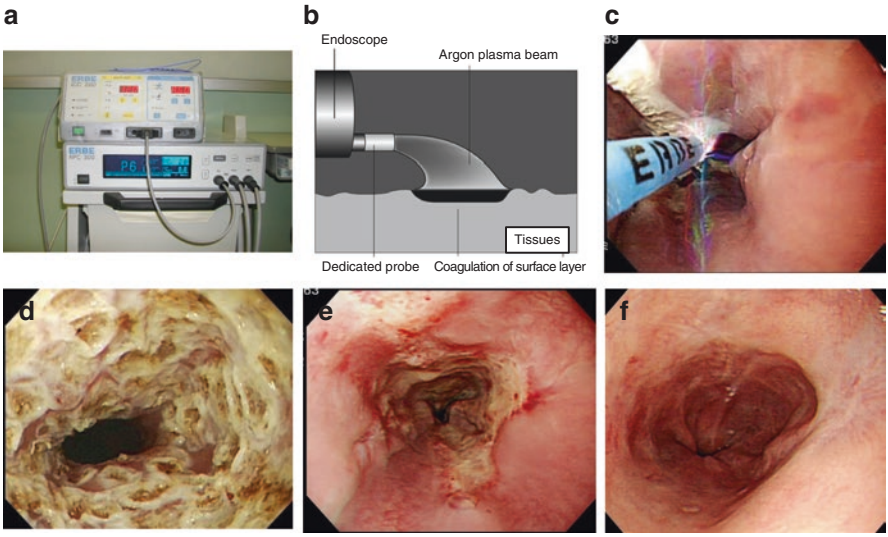


Fig. 25.1 APC consolidation procedure. (**a**) The APC system. (**b**, **c**) The argon gas emitted from the probe is blown onto the tissue, and the coagulating current is conducted through the gas like a spray to coagulate the tissue. The output power is 40 W, and the argon gas flow is 1 L/min. (**d**) The lower esophagus is cauterized circumferentially without leaving any space until it is covered with a shallow whitish ulcer. (**e**) Part of the shallow ulceration is still visible 1 week later. Additional treatment can be applied as required. (**f**) The ulcer appears scarred when observed 2 weeks later. *APC* argon plasma coagulation

endoscopes, has made it possible to utilize APC in endoscopic treatments of esophageal varices [4]. The APC system we use consists of an ERBE Erbotom ICC200 electrosurgical generator with an ERBE APC300 argon plasma coagulator and a dedicated disposable probe-emitting argon gas from its tip. The output power is 40 W, and the argon gas flow rate is 1 L/min. The argon gas emitted from the probe is blown onto the tissue, and the coagulating current is conducted through the gas like a spray to coagulate the tissue (Figs. 25.1 and 25.2).

When the esophageal varices, their feeding veins, and the surrounding small veins disappear as a result of the EIS using the EO-AS combination method, the APC consolidation can be applied. The lower esophageal mucosa is treated circumferentially by means of the APC technique to form a circumferential ulcer and to replace the mucosal and submucosal layers with a mass of dense fibrous tissues. The goal of this treatment is to prevent recurrence by hardening the breeding bed for the varices (Fig. 25.3) [8, 9].

25.3 Validation of Consolidation Methods Following the EO-AS Combination Therapy

Chronological changes in the 1st to 3rd layers of the esophageal wall were observed in 19 cases where EUS examination was performed before and after treatment with the EO-AS combination therapy followed by AS consolidation [2, 10]. The controls

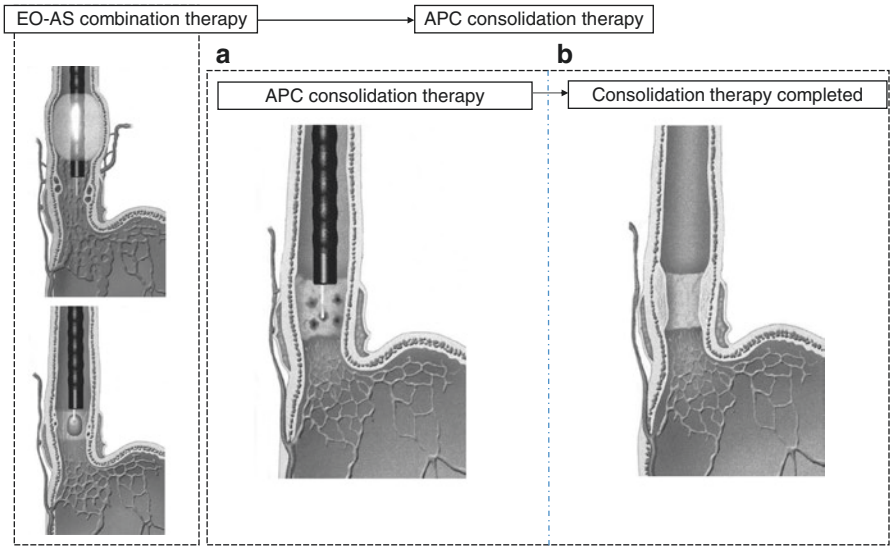


Fig. 25.2 EO-AS combination therapy followed by APC consolidation therapy. (**a**) Following EO-AS combination therapy, apply APC circumferentially on the lower esophagus to form a circumferential ulcer. (**b**) When the ulcer has healed, the esophageal wall will be replaced by thick fibrous tissues (sclerosis). *EO* ethanolamine oleate, *AS* aethoxysklerol, *APC* argon plasma coagulation

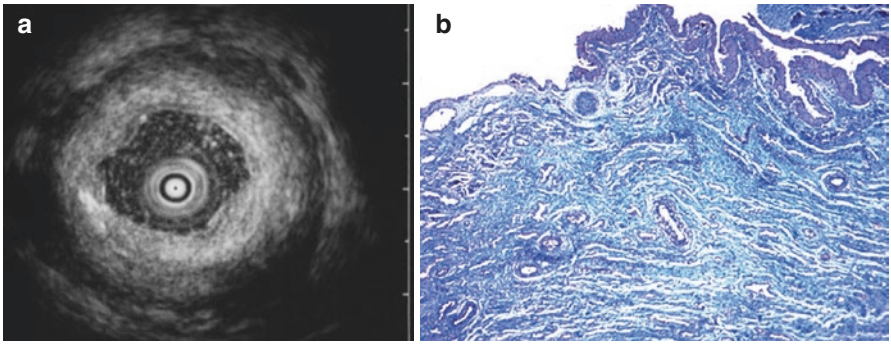


Fig. 25.3 EUS and histopathological findings after application of APC consolidation (autopsied case). (**a**) The esophageal mucosa and submucosa are amorphous and have thickened. No small blood veins can be seen in the wall. (**b**) The esophageal mucosa and submucosa have been replaced with dense fibrous tissues. No development of new blood veins is observed. Sclerosis of the esophageal wall has been made to eliminate the breeding ground for esophageal varices, preventing a recurrence. *EUS* endoscopic ultrasonography, *APC* argon plasma coagulation

were 19 patients with healthy esophagus (Table 25.1). In the EUS findings 1 week after consolidation therapy, 1st to 3rd layers (equivalent to mucosa-submucosa layers) were significantly thickened so that it was difficult to distinguish each layer, and ultrasound produced a low echoic parenchymal pattern. This was caused by

Table 25.1 Chronological EUS observation of the esophageal wall thickness after AS consolidation following EO-AS combination therapy

Period after treatment (n = 19)	1st–3rd layer (mucosa-submucosa)/mm (mean thickness/mm)	4th layer (muscle layer)/mm (mean thickness/mm)	1st–4th layer (mucosa-muscle layer) (mean thickness/mm)
1–3 (weeks)	3.0–9.0 (5.0)	0.6–3.1 (1.7)	5.0–10.0 (6.7)
6–12 (months)	3.0–3.5 (3.2)	0.5–2.2 (1.3)	4.0–5.0 (4.5)
14–19 (months)	2.0–4.0 (3.0)	0.8–2.0 (1.2)	3.0–6.0 (4.2)
Normal esophagus (n = 19)	0.9–1.3 (1.0)	0.5–1.0 (0.7)	1.4–2.0 (1.7)

EUS endoscopic ultrasonography, *AS* aethoxysklerol, *EO* ethanolamine oleate

inflammatory changes, which also generated a tentative sense of constriction. By approximately 1 month after the consolidation therapy, the inflammatory changes were completely replaced with fibrous tissues, following which high echoic EUS images of the 1st to 3rd layers were observed for a long period. Compared with a normal esophagus, the esophageal wall treated using the consolidation method remains thick for a long time, resulting in the effective prevention of esophageal variceal recurrence.

Obara et al. compared the thickness of the esophageal wall observed with EUS and the incidence of recurrence in 11 patients who received laser consolidation with those in 57 patients who received AS consolidation after EO-AS combination therapy [3]. The mean thickness of esophageal wall after consolidation was 6.3 mm in the laser group and 6.4 mm in the AS group. No recurrence was observed in the laser group (follow-up period of 3–17 months), while recurrence was observed in two (3.5%) patients in the AS group (follow-up period of 1–4 years). In addition, esophageal constriction was not observed in the laser group. These results showed that both laser and AS consolidation were equally effective in preventing variceal recurrence after EO-AS combination therapy and that laser consolidation was also free from esophageal constriction.

Kikuchi et al. [11] reported on chronological changes in the esophageal wall in 21 patients treated using the APC consolidation method and on pathological findings in 1 autopsied case. According to the report, the submucosa of the esophageal wall in particular remained thickened for more than 1 year after APC consolidation therapy. The cumulative recurrence rate after 2 years was 13.8%. Furthermore, pathological findings from the autopsied esophageal wall 2 weeks after APC consolidation therapy showed that inflammation occurred not only in the mucosa but also in the submucosa as well as partially in the muscularis propria, where it formed granulation tissue. Obara et al. [10] also reported that AS consolidation partially affected the muscularis propria because slight thickening of the 4th layer of the esophageal wall was observed, indicating effective recurrence prevention.

25.4 APC Irradiation Procedure Following EVL-AS Combination Therapy

As EIS using EO is contraindicated in patients with Child-Pugh grade C, TBIL 4 mg/dL, or more, EVL can be combined with EIS using AS in order to reduce the high rate of variceal recurrence after EVL. Using this EVL-AS combination method, rubber O-rings are placed densely onto the esophageal varices located between the esophagogastric junction and the lower esophagus. A week later, 1–2 mL of 1% AS per point is injected into the mucosa in the clearances made between the regions treated using EVL (Fig. 25.4).

Although the Obara consolidation method was originally applied using AS or a laser following EO-AS combination therapy where feeding veins are obliterated, the APC consolidation method following EVL was also introduced and performed to prevent rebleeding or recurrence within a short period [12]. APC consolidation after EVL-AS combination therapy is a procedure in which the normal lower esophageal mucosae located between the ulcers formed after EVL-AS combination therapy are cauterized using APC. This method has also been performed to date and can make it possible to avoid bleeding to death in cases with severe hepatic disorder or advanced HCC.

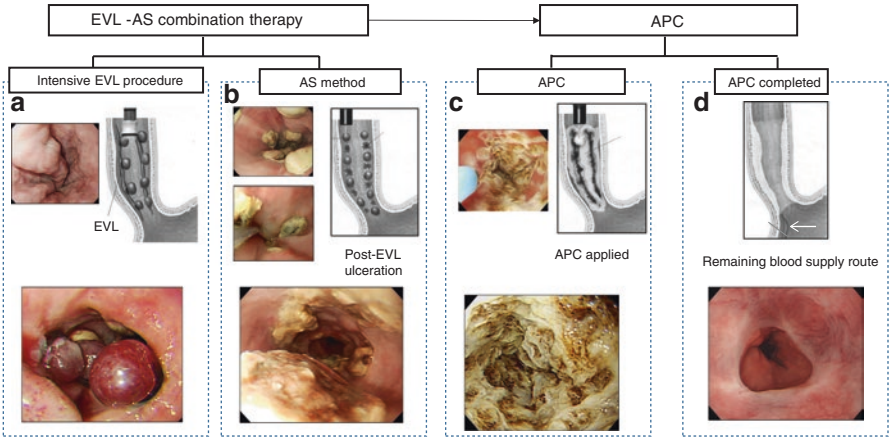


Fig. 25.4 EVL-AS combination therapy followed by APC. (**a**) A dense array of rubber O-rings are hooked onto the esophageal varices located from the esophagogastric junction to the lower esophagus. (**b**) AS is injected into the mucosa between ulcers formed after EVL so that the mucosa will bulge. (**c**) The remaining mucosa in the lower esophagus (except for the ulcers formed by the AS method) is cauterized circumferentially and uniformly with APC. (**d**) As the circumferential ulcers heal, the esophageal wall is replaced with thick fibrous tissue, but the blood supply route remains patent. *EVL* endoscopic variceal ligation, *AS* aethoxysklerol, *APC* argon plasma coagulation

25.5 Outcomes of Consolidation Therapy

Obara et al. [12] reported the outcomes and 5-year prognosis of employing various treatment regimes, namely, the EO-AS combination therapy alone, the EO-AS combination therapy with AS consolidation, the EO-AS combination therapy with laser consolidation, and the EVL-AS combination therapy with laser irradiation (Table 25.2). Compared with the EO-AS combination therapy alone, a greater number of treatment sessions were conducted using AS or laser consolidation. However, recurrence rates were significantly lower (in particular, the bleeding recurrence rate was 0%), and the recurrence-free period was typically longer in cases where AS or laser consolidation was additionally applied following EO-AS combination therapy.

Obara et al. [9] also found that the cumulative nonrecurrence rates after EO-AS combination therapy followed by laser consolidation were as high as 95.2% after

Table 25.2 Outcomes and prognosis after 5 years of employing four different treatment regimes

Treatment method	EIS (EO-AS combination therapy)	EO-AS combination therapy + AS consolidation	EO-AS combination therapy + laser consolidation	EVL-AS combination therapy + laser irradiation
No. of cases	86	70	63	24
Total no. of sessions for complete eradication (times)	4.2	9.1	9.2	7.6
Complication of esophageal stricture (%)	3.4	28.1	0	4.2
Esophageal wall thickness at completion of treatment with EUS (mm)	Irregular thickening 2.0–3.0	Circumferential thickening 6.4	Circumferential thickening 6.1	Irregular thickening 4.0–6.0
Non-bleeding recurrence rates (%)	31.4	7.1	7.9	37.5
Bleeding recurrence rates (%)	10.5	0	0	8.3
Recurrence-free period (months)	17.2	27.2	19.0	4.7

EO ethanolamine oleate, *AS* aethoxysklerol, *EIS* endoscopic injection sclerotherapy, *EVL* endoscopic variceal ligation, *EUS* endoscopic ultrasonography

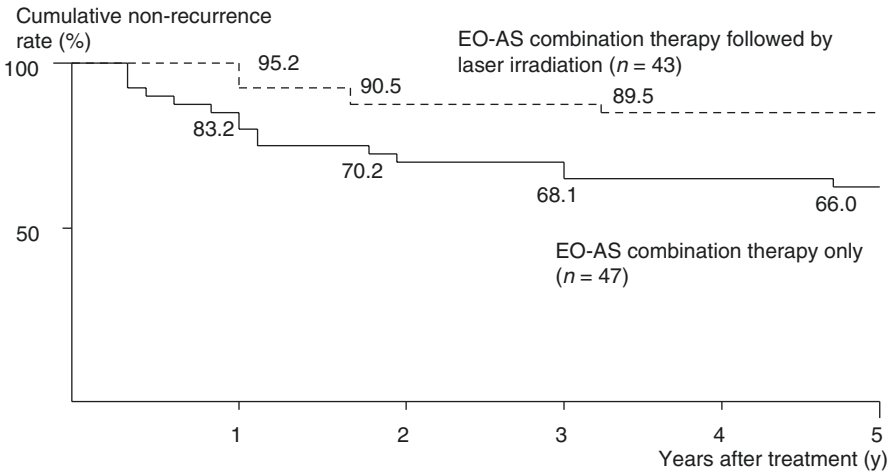


Fig. 25.5 Cumulative nonrecurrence rates in patients treated with the EO-AS combination therapy followed by laser consolidation in which esophageal varices were completely eliminated. *EO* ethanolamine oleate, *AS* aethoxysklerol

1 year, 90.5% after 3 years, and 89.5% after 5 years (Fig. 25.5). The recurrent cases were F0, RC-positive esophageal varices [13, 14] without bleeding and could be treated on an outpatient basis. By comparison, for cases treated using the EO-AS combination method alone, the rates were 83.2% after 1 year, 68.1% after 3 years, and 66.0% after 5 years. The recurrent cases were F1–F2, RC-positive esophageal varices, and bleeding was observed in about 10% of these cases. All the recurrent cases required inpatient treatment. Accordingly, the nonrecurrence rates were significantly higher in the cases treated using laser consolidation than in those treated with the EO-AS combination method alone.

Deguchi et al. [15] reported that cumulative recurrence rates in 124 patients treated using the EO-AS combination method alone were 29.0% after 1 year and 34.7% after 2 years, which were significantly higher than the 9.7% after 1 year and 11.3% after 2 years in 62 patients treated using the EO-AS combination method followed by APC consolidation. APC consolidation after the EO-AS combination therapy was found to be safe and significantly prevented the recurrence of esophageal varices. Harras et al. [16] divided 200 patients with bleeding esophageal varices into four groups and compared the recurrence rates of the four different regimes. Recurrence rates at 18 months after treatment were 2% in the scleroligation group, 4% in the EVL plus APC group, 14% in the EIS using EO group, and 28% in EVL-alone group, which indicated the efficacy of APC for recurrence prevention.

Matsui et al. [17] compared the efficacy of the consolidation therapy using APC with that using AS and reported that the accumulated nonrecurrence rates after 1 and 2 years were 93.3% and 84.0% in APC group and 87.9% and 76.9% in AS group, respectively. Both therapies were equally effective for preventing recurrence; however, esophageal constriction was observed in 8.8% of the AS group, and APC required fewer treatment sessions than AS consolidation.

25.6 Conclusion

Treatment of esophageal varices using EO-AS combination therapy followed by AS, laser, or APC consolidation has been shown to be safe for patients and effective in preventing further variceal recurrence. Although the efficacy of those three consolidation methods is comparable, APC consolidation is currently the most widely applied because AS consolidation generates esophageal stricture in some cases, and laser devices are expensive. In cases where EO is contraindicated but consolidation can be performed taking into consideration the patients' condition, APC consolidation following EVL-AS combination therapy is effective.

References

1. Obara K, Masaki M, Sakamoto H, Iwasaki K, Mitsuhashi H, Orikasa K, et al. Studies on prognosis of patients with esophageal and gastric varices treated with injection sclerotherapy using EO or EO-AS combination method. Gastroenterol Endosc. 1987;29:2232–6. [in Japanese with English abstract].
2. Obara K, Ohira H, Sakamoto H, Iwasaki K, Mitsuhashi M, Suzuki S, et al. A new method of sclerotherapy for esophagogastric varices: EO-AS combination method followed by mucosa-fibrosis with AS. Gastroenterol Endosc. 1981;31:2977–81. [In Japanese with English abstract].
3. Obara K, Kojima T, Irisawa A, Watanabe S, Kuwana T, Kogure A, et al. A new method of sclerotherapy for esophageal varices: EO-AS combination method followed by mucosa-fibrosing with laser. Gastroenterol Endosc. 1994;36:716–21. [In Japanese with English abstract].
4. Grund KE, Storek D, Farin G. Endoscopic argon plasma coagulation (APC): first clinical experiences in flexible endoscopy. Endosc Surg Allied Technol. 1994;2:42–6.
5. Obara K, Toyonaga A, Kokubu S. Guidelines for the endoscopic treatment of esophagogastric varices. In: Society for Japanese Gastroenterological Endoscopy, editor. Guidelines for gastrointestinal endoscopy. 3rd ed. Tokyo: Igaku-Shoin; 2006. p. 215–34. [in Japanese].
6. The Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer, second English edition. Tokyo: Kanehara & Co., Ltd.; 2003.
7. Irisawa A, Saito A, Obara K, Shibukawa G, Takagi T, Shishido H, et al. Endoscopic recurrence of esophageal varices is associated with the specific EUS abnormalities: severe periesophageal collateral veins and large perforating veins. Gastrointest Endosc. 2001;53:77–84.
8. Obara K. Endoscopic EV treatment. Endoscopic treatment of esophagogastric varices. Tokyo: Narunia Inc.; 2016. p. 21–46.
9. Obara K. Endoscopic injection sclerotherapy followed by mucosal fibrosis. JJPH. 2002;8:128–35. [In Japanese].
10. Obara K, Kasukawa R. Endoscopic ultrasonography for evaluation of patients treated by endoscopic injection sclerotherapy. Endosc Digest. 1990;2:1395–403. [In Japanese with English abstract].
11. Kikuchi Y. Pathological change of esophageal wall after argon plasma coagulation therapy for esophageal varices. JJPH. 2003;9:73–7. [in Japanese].
12. Obara K. Esophagogastric varices: indication, treatment procedure and outcomes. J Jpn Soc Intern Med. 2003;92(1):58–65. [In Japanese].
13. Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc. 2010;22(1):1–9. https://doi.org/10.1111/j.1443-1661.2009.00929.X.

14. The Japan Society for Portal Hypertension. The general rules for study of portal hypertension. 3rd ed. Tokyo: Kanehara & Co., Ltd; 2013. p. 37–62. [in Japanese].
15. Deguchi H, Kato J, Maeda Y, Moribata K, Shingaki N, Niwa T, et al. Argon plasma coagulation is effective for prevention of recurrent esophageal varices after endoscopic injection sclerotherapy: single-center case-control study. Dig Endosc. 2016;28:42–9. https://doi.org/10.1111/den.12538.
16. Matsui S, Kudo M, Nakaoka R, Shiomi M. Effect of mucosa-fibrosing therapy with argon plasma coagulation on esophageal varices. JJPH. 2003;8:180–4. [In Japanese with English abstract].
17. Harras F, Sheta S, Shehata M, Saadany S, Selim M, Mansour L. Endoscopic band ligation plus argon plasma coagulation versus scleroligation for eradication of esophageal varices. J Gastroenterol Hepatol. 2010;25:1058–65. https://doi.org/10.1111/j.1440-1746.2010.06265.x.

Chapter 26
Endoscopic Treatment of Esophageal Varices: Eradicative Endoscopic Variceal Ligation

Shigeru Nakano and Yoshinori Igarashi

Abstract Eradicative endoscopic variceal ligation (eEVL) is a simple and safe procedure for eradication of esophageal varices via repeated EVL. Controlling the influx of blood into the lower esophagus via multiple ligations decreases the rate of recurrence. Over the past 20 years, the average frequency of variceal recurrence after eEVL was satisfactory with 1- and 3-year nonrecurrence rates of 90.8% and 73.6%, respectively. The univariate analysis indicated that the red color sign remaining at the end of the second session of EVL, male sex, and Child-Pugh class C were factors associated with recurrence.

Keywords eEVL · Esophageal varices · Repeated EVL

26.1 Introduction

First reported by Stiegmann et al. in 1986 [1], endoscopic variceal ligation (EVL) was rapidly adopted in Japan as it is simple and safe, but it has been subject to criticism on account of its high recurrence rate. Eradicating the varices via endoscopic injection sclerotherapy can reduce the recurrence rate, and it is expected that the recurrence rate can be reduced even via EVL alone. In 1995, Kondo et al. developed eradicative EVL (eEVL) in which ligation is repeated multiple times to eradicate the varices using only EVL [2].

S. Nakano (✉) · Y. Igarashi
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University, Omori Medical Center, Tokyo, Japan
e-mail: nakano-s@med.toho-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_26

26.2 Methods

As O-rings are placed in a spiral fashion using the original method of Stiegmann et al., the blood vessels of the submucosal layer where the varices originate are preserved, and the blood flowing into the varices does not stop. This is the main reason for the unsatisfactory treatment results, and why additional measures, such as controlling of the blood flow and eradication of the originating location, are necessary. Multiple ligations are performed each time in eEVL, and the treatment ends when the varices are eradicated. Multiple ligations reduce the submucosal blood flow and create fibrosis, thus inhibiting recurrence [3, 4]. Figure 26.1 shows the procedure.

First-time treatment: Identifying the feeding vein of the varices and performing ligations as close as possible from the stomach-side mucosa of the esophagogastric junction. The treatment is stopped once the hypoplastic site of the varices is reached because sufficient suction will not be possible. Ligation is usually performed at 10–16 sites depending on the extent of the varices.

Second and subsequent treatments: The procedure is selected on the basis of the remaining varices. According to the general rules for recording the endoscopic findings of esophagogastric varices[5], close ligation is performed and aimed at the blockage of the feeding vein as in the first-time treatment, and blood flow from the portal vein to the lower esophagus is inhibited as much as possible in cases of F2 or greater. Moreover, ligation is performed not only for the varices but also for the healthy mucosa where new varices may form in cases of F1 or F0RC1.

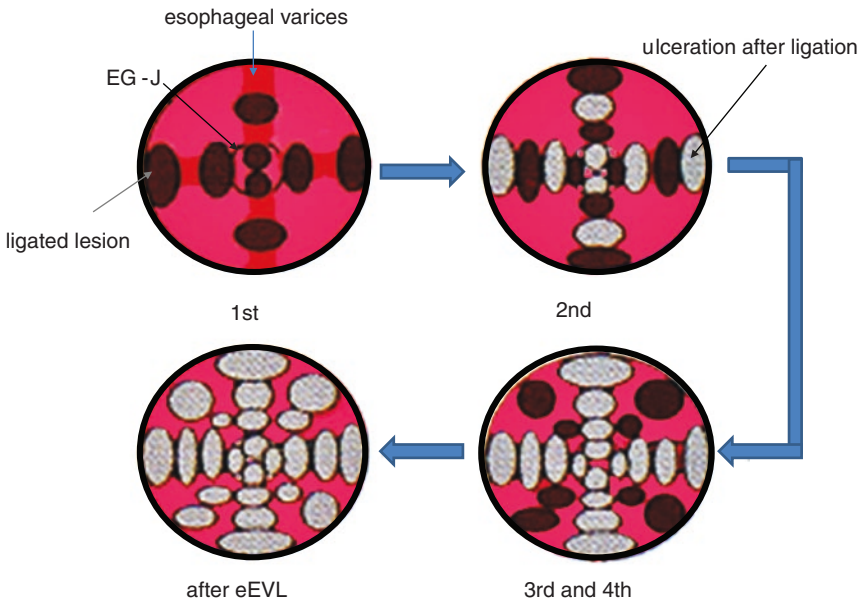


Fig. 26.1 Method of eradicative endoscopic variceal ligation

The goal of treatment is to achieve eradication (F0RC0) usually via repeat ligations performed 3 to 4 times. In some cases, more ligations may be required.

At our institute, the treatment interval was initially 2 weeks, but 4 to 6 weeks interval has been used since 2002. The increased treatment interval allows patients to be discharged and return to normal life. The esophageal mucosa are then be in a better state for subsequent treatments, and even the nutritional status of the patients improves.

26.3 Changes in Vessel Construction Before and After Treatment

The blood vessel construction around the varices was examined using endoscopic ultrasonography and percutaneous transhepatic portography before and after eEVL. After treatment, changes were observed not only in the ligation sites of the lower esophagus but also in the blood vessel construction up to the cardiac venous plexus [3, 4]. Greater blood flow reduction was observed upstream via ligation of the lower esophagus, which is considered to contribute to lower recurrence rates than conventional EVL.

26.4 Results

We followed up and retrospectively studied 289 of 406 cases treated with EVL at our department between April 1, 1995, and March 31, 2010. Table 26.1 shows an

Table 26.1 Characteristics of the study group

No. of patients		289
Age (years, Mean, SD)		62 ± 10
Male		202 (70%)
Etiology of cirrhosis		
Virus		129
Alcohol		116
Others		44
Child-Pugh grade A/B/C		120/139/30
Prior gastrointestinal bleeding		92 (32%)
No. of EVL sessions (Mean, SD)		3.1 ± 0.9
No. of banding sites (Mean, SD)		42.2 ± 11.6
Observation period (Month, Mean, SD)		35 ± 34
Complication	Bleeding	5
	Stenosis	1

overview of the cases. The average number of EVL sessions was 3.1; however, the standard deviation was high (0.93). The standard deviation of age was also high, indicating that the population was heterogeneous. Mild complications were observed, i.e., postoperative bleeding in five cases and stenosis in one case.

Statistical analyses were performed using the EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria) and is a modified version of R Commander designed to add statistical functions frequently used in biostatistics [6].

The treatment results were examined by defining rebleeding or endoscopic findings as the presence of F2 or greater or RC-positive finding as recurrence. For all 289 cases, the median period of nonrecurrence was 72 months, with 1- and 3-year nonrecurrence rates of 90.8% and 73.6%, respectively (Fig. 26.2).

In the univariate analysis, a significant difference was observed in male, treatment number of EVL sessions **4**≦, and presence of RC sign at the end of the second EVL session as factors that increased the recurrence rate. There was a tendency that the recurrence rate was high, although there was no significant bleeding history and Child-Pugh grade C (Table 26.2). An analysis using the proportional hazard model was performed using factors with significant differences and trends in the univariate analysis. Sex, Child-Pugh grade C, and existence of RC sign at the end of the second EVL session were selected. The number of EVL sessions or bleeding history was

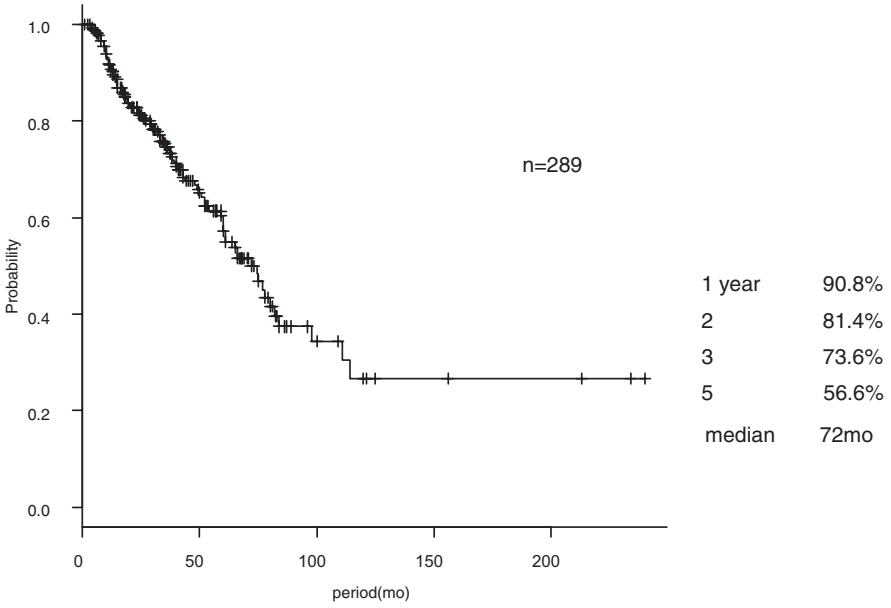


Fig. 26.2 Overall nonrecurrence rates

not selected for the model (Table 26.3).

Table 26.2 Kaplan-Meier estimation

		n	5 Years non-recurrence rate (%)	*P* value
Sex	Male	202	50.0	0.0145
	Female	87	70.2	
Child-Pugh	A or B	259	57.3	0.023
	C	30	38.9	
Etiology	Alcohol	116	49.9	0.62
	Virus	129	58.5	
	Others	44	69.5	
Bleeding history	Yes	89	41.3	0.079
	No	200	58.5	
F factor before treatment	F2 or smaller	240	56.4	0.27
	F3	49	53.3	
Therapy period	Before 2002	92	60.0	0.45
	After 2002	197	54.1	
Session of EVL	4≧	271	59.7	0.0074
	5≦	18	36.3	
F2 after 2nd EVL	Yes	18	44.9	0.227
	No	271	58.5	
RC after 2nd EVL	Yes	49	35.6	0.0097
	No	240	63.9	

Table 26.3 Cox's proportional hazard model

		Hazard ratio	*p* value
Sex	Male	1.7	0.041
	Female		
Child-Pugh	A or B	1.8	0.078
	C		
RC after 2nd EVL	Yes	2.4	0.00032
	No		

26.5 Conclusion

Increased risk of recurrence when multiple ligations are required, and RC signs remaining positive after ligation, indicate some of the limitations of EVL. However, the proportion of such cases is small, with most other cases having favorable outcomes. Various methods can be selected for the endoscopic treatment of esophageal varices; among which, eEVL is one of the simplest and easiest procedures. Although this procedure is easy to implement, we emphasize that it is important to repeat EVL until eradication of the varices is endoscopically confirmed to prevent variceal recurrence.

References

1. Stiegmann GV, Cambre T, Sun JH. A new endoscopic plastic band ligative device. Gastrointest Endosc. 1986;32:230–3.
2. Kondo E, Ishihara M, Koyama H, et al. Adapting endoscopic variceal ligation using numeraus o-rings for esophageal varices. [in Japanese]. Gastroenterol Endosc. 1995;37:2812–21.
3. Nakano S, Hachiya A. Effect of endoscopic variceal ligation for esophageal varices: vascular structure images by miniature ultrasound probe. Dig Endosc. 2005;17:203–9.
4. Matsuzaki H, Kondou E, Kurita T, et al. Comparison of percutaneous transhepatic portograms obtained before and after eradicative endoscopic variceal ligation of esophageal varices. Gastroenterol Endosc. 1997;39:643–9. (in Japanese with English abstract).
5. The Japan Society for Portal Hypertension, editor. The general rules for study of portal hypertension. 2nd ed. Tokyo: Kanehara Co.; 2004. p. 37–50.
6. Kanda Y. Investigation of the freely-available easy-to-use software "EZR" (Easy R) for medical statistics. Bone Marrow Transplant. 2013;48:452–8. https://doi.org/10.1038/bmt.2012.244. Advance online publication 3 December 2012.

Chapter 27
Endoscopic Treatment of Esophageal Varices: Bimonthly Endoscopic Variceal Ligation

Hiroshi Yoshida, Hiroshi Makino, Tadashi Yokoyama, Hiroshi Maruyama, Atsushi Hirakata, Junji Ueda, Hideyuki Takata, Yasuhiro Mamada, Nobuhiko Taniai, and Eiji Uchida

Abstract Endoscopic variceal ligation (EVL) is being used increasingly to treat esophageal varices because of its safety and simplicity and because no sclerosant is required. However, early recurrence of esophageal varices after this procedure has been reported.

We compared the efficacy and long-term results of EVL performed in three treatments using a total of 16 O-rings at two different intervals, namely, biweekly (once every 2 weeks: the conventional interval) and bimonthly (once every 2 months). In all patients except two (both in the biweekly group), the esophageal varices were completely eradicated. Overall rates of both variceal recurrence and additional treatment were higher in the biweekly group than in the bimonthly group ($P < 0.001$).

EVL performed bimonthly in three treatment sessions for esophageal varices yielded better results than the same treatment performed biweekly. Treatment at the longer interval yielded a higher total eradication rate, lower recurrence rate, and lower rate of required additional treatment. Repeat treatment of EVL is useful; therefore, three treatment sessions should be considered as one course. Bimonthly EVL (three times in 4 months) might become a standard treatment for esophageal varices.

Keywords Bimonthly EVL · Endoscopic variceal ligation (EVL) · Esophageal varices · Repeat treatment

H. Yoshida (✉) · Y. Mamada · E. Uchida
Department of Surgery, Nippon Medical School Hospital, Tokyo, Japan
e-mail: hiroshiy@nms.ac.jp

H. Makino · T. Yokoyama · H. Maruyama · A. Hirakata · J. Ueda · H. Takata
Department of Surgery, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan

N. Taniai
Department of Surgery, Nippon Medical School Musashi Kosugi Hospital, Tokyo, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_27

27.1 Introduction

Recently, endoscopic treatments have been developed to treat esophageal varices. Two endoscopic techniques are used for this purpose, namely, endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL) [1–7]. EIS can be performed either intravaricealy or extravaricealy [2–4, 8]. Intravariceal EIS obliterates the veins feeding the esophageal varices and the interconnecting perforating veins. Extravariceal EIS achieves local eradication, but, like EVL, it does not obliterate the interconnecting perforating or feeder vessels. Occasionally, EIS is associated with local and systemic complications due to use of the sclerosant [1]. EVL is increasingly being used instead of EIS because of its safety and simplicity without complications associated with EIS. However, although EVL achieves local eradication, it does not completely obliterate the veins feeding the esophageal varices [9]; therefore early recurrence after EVL has been reported [2].

Here, we investigated whether the use of multiple EVL treatment sessions at bimonthly interval could reduce the recurrence rates of esophageal varices compared with those treated at biweekly interval.

27.2 Method

Previously, we reported differences between the responses of recurrent esophageal varices to EVL alone and to EVL plus extravariceal EIS [8]. The overall rate of variceal recurrence was higher after EVL alone than after EVL plus extravariceal EIS. However, the number of subsequent hospitalizations for additional treatments was lower after EVL alone (1.8 hospitalizations) than after EVL plus extravariceal EIS (2.9 hospitalizations). Therefore, in this study, we administered three EVL treatment sessions as one course.

27.2.1 EVL Interval

Conventionally, we have performed EVL treatments once every 2 weeks (biweekly), and a total of three treatment sessions are often required. However, we considered that using a longer interval between EVL treatment sessions might improve the efficacy of treatment for esophageal varices. Previously, we reported that the rate of bleeding of incompletely eradicated esophageal varices was high, but that early bleeding (within 5 months after endoscopic treatment) was rare [3]. We therefore

speculated that three treatment sessions at bimonthly intervals (i.e., with the third session 4 months after the first) might be sufficient to prevent bleeding of the varices. Here, we compared the short- and long-term results of EVL performed in three sessions, using a total of 16 O-rings per patient, at two different intervals, namely, biweekly (once every 2 weeks: the conventional interval) and bimonthly (once every 2 months).

In the biweekly group (n = 32), the esophageal ulcers resulting from the first and second EVL sessions had not completely healed by the time of the third session. In the bimonthly group (n = 31), all of the treatment-created esophageal ulcers had completely healed by the time of the next treatment session. Esophageal varices were completely eradicated in all patients, with the exception of two in the biweekly group. Esophageal varices recurred in 24 patients (80.0%) over a mean follow-up of 28.9 ± 12.6 months in the biweekly group and in 18 patients (58.1%) over a mean follow-up of 33.0 ± 15.6 months in the bimonthly group. The 1- and 2-year cumulative recurrence rates among the patients with complete eradication were 66.7% and 82.2% in the biweekly group and 9.8% and 57.1% in the bimonthly group. The 1- and 2-year cumulative rates of additional treatments among the patients with recurrent varices after complete eradication were 67.0% and 82.4% in the biweekly group and 9.9% and 57.4% in the bimonthly group. The overall rates of variceal recurrence and the number of required additional treatment sessions were both higher after biweekly EVL than after bimonthly EVL ($P < 0.001$). We concluded that EVL once every 2 months has better outcomes than EVL once every 2 weeks in patients with esophageal varices. Treatments performed bimonthly had a higher rate of complete eradication and lower rates of recurrence and required additional treatment [6].

27.2.2 Bimonthly EVL Procedure

Following premedication, the endoscope is introduced with a flexible endoscopic sheath. The endoscope is then removed and attached to a pneumatically activated EVL device (Sumitomo Bakelite, Tokyo, Japan). The endoscope is reinserted, and suction is maintained on the varix. As the varix is pulled into the ligator cap, air is injected into the tube to achieve EVL.

At the first treatment session, all varices from the gastroesophageal junction oralwards are ligated. Each varix is ligated with one or two bands. EVL is performed every 2 months. During the second and third sessions, any remaining varices receive EVL [6].

One course of bimonthly EVL consists of three EVL treatment sessions over the course of 4 months.

27.3 Patients Management After EVL

After EVL, the patient should fast for 24 hours and be observed closely for complications, such as hemorrhage (caused by incision from the bands), sloughing of the bands (leading to early bleeding recurrence), fever, and a localized choking sensation. Prophylactic antibiotics are given to all patients for 3 days. The antibiotic dosage is adjusted on the basis of the results of sensitivity testing in patients confirmed to have an infection.

Anti-ulcer drugs, such as mucosal protective drugs, H2 blockers, and proton pump inhibitors, are given for esophageal ulceration resulting from EVL. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, because their use violates the integrity of the esophagogastric mucosa. Use of NSAIDs is an important risk factor for variceal hemorrhage [10].

27.4 Follow-Up

Three months after one course of bimonthly EVL, we performed an endoscopic evaluation to assess the completeness of the eradication. Follow-up endoscopy was then performed at 6–2-month intervals (Figs. 27.1 and 27.2).

27.5 Discussion

To treat varices by intravariceal EIS, blockage of flow in the left gastric vein by injection of a sclerosing agent via esophageal varices is considered to provide better long-term results [11]. Extravariceal EIS and EVL both achieve local eradication, but they do not completely obliterate the interconnecting perforating and feeder vessels [2]. Insufficient blockage of blood flow from the left gastric vein to the lower esophagus may lead to relapse of varices [12]. Lo et al. [13] reported that portal pressure is reduced after EVL whenever there is extensive shunt formation. When blood from the varices enters the azygos vein at the distal esophagus, the esophageal varices are less prominent [14]. Blocking of the blood flow in the varices in the course of multiple EVL treatments promotes the flow of blood into the azygos vein via the paraesophageal veins or other shunts (Figs. 27.3 and 27.4). Local treatments

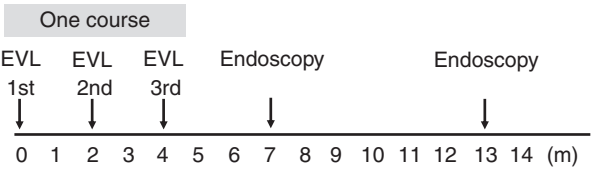


Fig. 27.1 Method used for bimonthly EVL

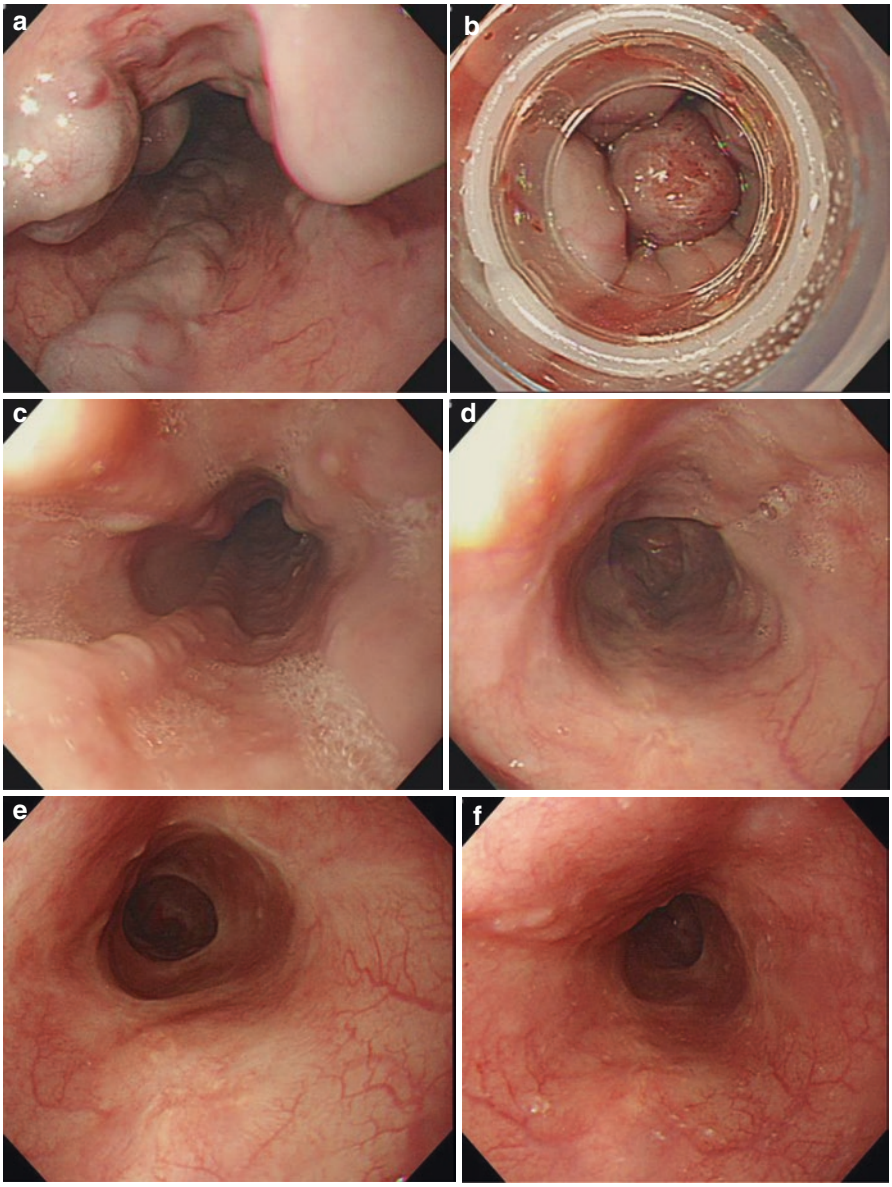


Fig. 27.2 Endoscopic findings: before treatment (**a**); just after the first treatment session (**b**); before the second treatment session (**c**); before the third treatment session (**d**); 1 year after the end of the complete course of treatment (**e**); 2 years after the end of the complete course (**f**)

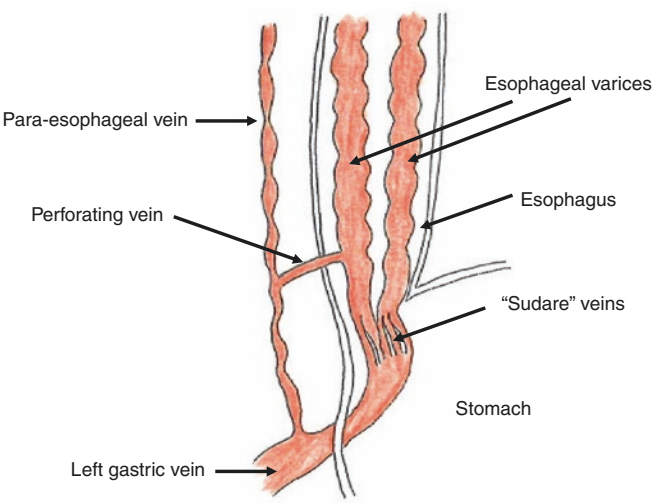


Fig. 27.3 Anatomical schema of esophageal varices

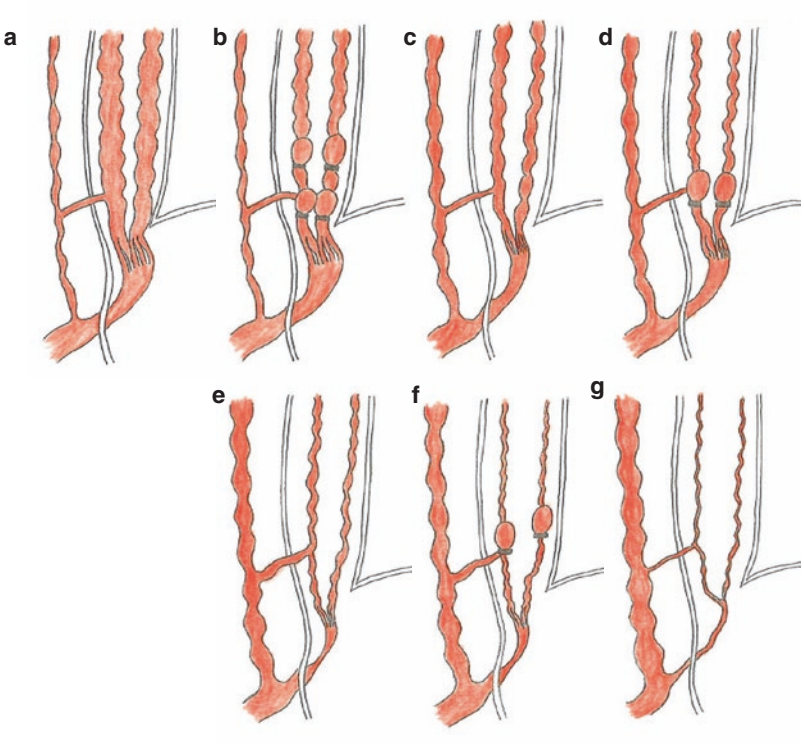


Fig. 27.4 Schema of hemodynamic changes after bimonthly EVL: before treatment (**a**); just after the first treatment session (**b**); before the second treatment session (**c**); just after the second treatment session (**d**); before the third treatment session (**e**); just after the third treatment session (**f**); 3 months after the end of the course of treatment (**g**)

such as EVL achieve a reduction in variceal pressure through this mechanism. Therefore, use of a long interval between EVL treatment sessions may improve treatment efficacy.

27.6 Conclusion

EVL performed in three treatment sessions for esophageal varices at bimonthly intervals gave better results than the same treatments performed at biweekly intervals. Treatment at bimonthly intervals yielded a higher eradication rate, lower recurrence rate, and lower rate of required additional treatment. Repeat EVL is useful, and three treatment sessions should be considered as one course. Bimonthly EVL (three times over 4 months) has the potential to become a standard treatment for esophageal varices.

References

1. Masumori K, Onda M, Tajiri T, et al. Modified endoscopic variceal ligation. Dig Endosc. 1995;7:165–70.
2. Umehara M, Onda M, Tajiri T, Toba M, Yoshida H, Yamashita K. Sclerotherapy plus ligation versus ligation for the treatment of esophageal varices: a prospective randomized study. Gastrointest Endosc. 1999;50:7–12.
3. Tajiri T, Onda M, Yoshida H, et al. Endoscopic scleroligation is a superior new technique for preventing recurrence of esophageal varices. J Nippon Med Sch. 2002;69:160–4.
4. Yoshida H, Onda M, Tajiri T, et al. Endoscopic injection sclerotherapy for the treatment of reccurent esophageal varices after esophageal transection. Dig Endosc. 2002;14:93–8.
5. Yoshida H, Onda M, Tajiri T, et al. New techniques: combined endoscopic injection sclerotherapy and ligation for acute bleeding from gastric varices. Hepatogastroenterology. 2002;49:932–4.
6. Yoshida H, Mamada Y, Taniai N, et al. A randomized control trial of bi-monthly versus bi-weekly endoscopic variceal ligation of esophageal varices. Am J Gastroenterol. 2005;100:2005–9.
7. Sarin SK, Govil A, Jain AK, et al. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. J Hepatol. 1997;26:826–32.
8. Yoshida H, Tajiri T, Mamada Y, et al. Comparison of characteristics of recurrent esophageal varices after endoscopic ligation versus endoscopic ligation plus sclerotherapy. Hepatogastroenterology. 2004;51:457–61.
9. Hou MC, Lin HC, Kuo BI, Chen CH, Lee FY, Lee SD. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: a prospective randomized trial. Hepatology. 1995;21:1517–22.
10. Yoshida H, Mamada Y, Taniai N, et al. Interactions between anti-ulcer drugs and nonsteroidal anti-inflammatory drugs in cirrhotic patients with bleeding esophagogastric varices. Hepatogastroenterology. 2009;56:1366–70.
11. Takase Y, Shibuya S, Chikamori F, et al. Recurrence factors studied by percutaneous transhepatic portography before and after endoscopic sclerotherapy for esophageal varices. Hepatology. 1990;11:348–52.

12. Matumoto H, Matsutani S, Fukuzawa T, et al. Hemodynamics in the left gastric vein after endoscopic ligation of esophageal varices combined with sclerotherapy. J Gastroenterol Hepatol. 2001;16:495–500.
13. Lo GH, Liang HL, Lai KH, et al. The impact of endoscopic variceal ligation on the pressure of the portal venous system. J Hepatol. 1996;24:74–80.
14. Kimura T, Moriyasu F, Kawasaki T, et al. Relationship between esophageal varices and azygos vein evaluated by cineportography. Hepatology. 1991;13:858–64.

Chapter 28
Endoscopic Treatment of Esophageal Varices: Endoscopic Variceal Ligation Using a Multi-Band Ligator

Yoshiyuki Suzuki and Naoya Murashima

Abstract Endoscopic variceal ligation (EVL), a safe and effective treatment for esophageal varices, has undergone rapid progress since its invention. One of the greatest advantages of EVL over endoscopic injection sclerotherapy (EIS) is its versatile adaptability, particularly for high-risk populations such as elderly patients. Originally, the "Stiegmann-Goff Ligator Kit" (Bard Co., USA) used for the EVL procedure was equipped with a wire to remove the ligature bands from the endoscope. In Japan, the modified pneumo-activated EVL device (Sumitomo Bakelite Co. Ltd.) was invented and came into common use. These single-band ligators require an over-tube to ligate esophageal varices. However, we now use a multi-band ligator without an over-tube to perform ligations in rapid succession. This chapter contains an outline description of the multi-band ligator comparing with the single-band ligator.

28.1 Introduction

Esophagogastric varices are complications associated with portal hypertension. In many cases, patients exhibiting this form of clinical pathology also have an underlying chronic liver disease. Moreover, if hemorrhaging occurs, the patient's condition can deteriorate rapidly to the life-threatening condition [1–6]. There are many ways to treat esophagogastric varices, such as endoscopic treatment, surgery, interventional radiology (IVR), and medical treatment [7–9]. In recent years, however, the prevalence of esophagogastric varices in elderly patients with hepatoma has been overwhelming, creating the need for a safer and less invasive modality. In EVL,

Y. Suzuki (✉)
Department of Hepatology, Toranomon Hospital, Tokyo, Japan
e-mail: suzunari@interlink.or.jp

N. Murashima
Department of Gastroenterology, Mishuku Hospital, Tokyo, Japan
e-mail: murashima@mishuku.gr.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_28

esophageal mucosa adjacent to the variceal vessels is sucked into a cylindrical cap at the tip of the endoscope, and a ligature rubber band affixed to the periphery of the cylinder is released by means of a wire passing through the biopsy channel. The contraction of the ligature rubber band causes mechanical ligation of the vein and provokes necrosis. This chapter describes the advantages and disadvantages of applying EVL using a multi-band ligator, in which multiple bands are attached to the tip of the endoscope.

28.2 EVL Procedure Using a Multi-Band Ligator

A hood-shaped cylinder is attached to the tip of the endoscope, with multiple ligature bands arranged in an array outside the cylinder (Fig. 28.1). Generally, this structure contains between six and ten bands, and the penultimate band is colored differently, allowing EVL practitioners to see at a glance that the next band is the last one. The attached bands are removed using biopsy channel with a string-shaped thread or wire manipulated via a handle attached to the biopsy port (Fig. 28.2). Ordinarily, the device is rotated until a sound is produced, indicating that one ligature band has been released and that the vein under suction has been ligated. In EVL using a multi-band ligator, the treatment can be performed continuously without the need to repeatedly insert or remove the endoscope during the session. While it is not possible to feed water from the biopsy port, the opening to the side of the handle can be used for this purpose.

Fig. 28.1 The tip of an endoscope to which seven ligature bands are mounted. Six blue and one white bands are seen

Fig. 28.2 The operation unit of the multi-band ligator attached to the endoscope through the biopsy port. When the handle is rotated, the bands are released one by one to ligate the varix

28.3 Advantages and Disadvantages of EVL Using a Multi-Band Ligator

In this section, advantages and disadvantages of EVL using a multi-band ligator are described with reference to other modalities [10–16].

A single-band ligator can hold only one band per cylinder; therefore, cases involving the ligation of multiple varicose veins require the removal and reinsertion of the endoscope and the reattachment of the ligature band for each successive ligation. For this reason, the over-tube must be inserted. Carrying out multiple ligations following this procedure through an over-tube requires a considerable amount of time. This often causes increased discomfort to patients, with some cases requiring analgesia. Furthermore, use of an over-tube is contraindicated in patients with short physical stature, such as elderly women. Other problems associated with over-tubes

include recurrent laryngeal nerve paralysis and esophageal ulcers, which sometimes result in hemorrhage. On the other hand, insertion of a multi-band ligator may encounter some resistance at the pharynx, and patients often feel discomfort due to the attachment of the ligator to the tip of the endoscope. Once inserted, however, there are no other symptoms.

As the long cylinder of a multi-band ligator narrows the operator's visual field (Figs. 28.3 and 28.4), identifying the source of a bleeding in emergency cases is more difficult with this ligator than with a single-band ligator. In addition, because the biopsy channel is occupied, cleaning using water supplied through the biopsy

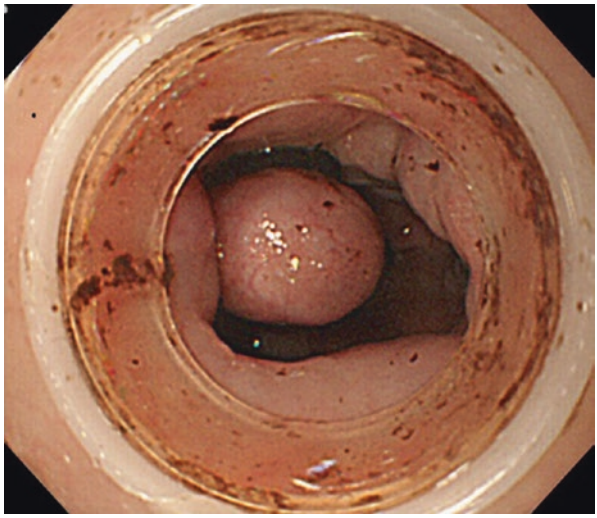


Fig. 28.3 The endoscopic image during EVL using the single-band ligator. The field of view is narrower than that obtained using an endoscope without a ligator kit

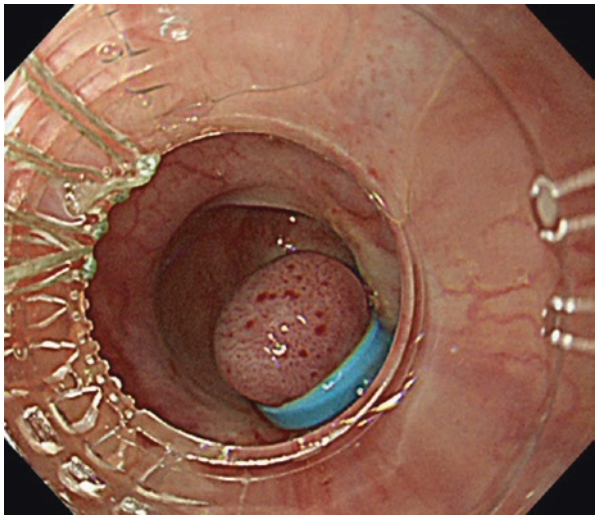


Fig. 28.4 The endoscopic image during EVL using the multi-band ligator. The field of view is narrower than that obtained during EVL using the single-band ligator

channel can be quite difficult. For these reasons, EVL using a multi-band ligator is not recommended for emergency endoscopy. The cylinder of a multi-band ligator is longer than that of a single-band ligator; therefore, additional care is necessary in order to avoid excessive suction of varicose veins, which can result in esophageal stenosis. Practitioners require ample skill and experience, because for complex procedures or cases where the endoscope is sharply rotated, ordinary operation may not generate sufficient torque, causing the ligated band to fall off. Inexperienced practitioners often encounter situations in which a single ligated band has slipped off or in which improper handle control causes multiple ligated bands to fall off at the same time.

28.4 Use in Actual Clinical Practice

The development of treatments for liver cirrhosis, hepatocellular carcinoma (HCC), and other ailments has clearly contributed to improved prognoses in patients suffering liver failure. In addition, the number of patients at high risk from varicose veins requiring treatment is increasing in step with the progress of the aging society [17]. EIS is not suitable for treating patients with Child-Pugh grade C, a severe hepatic disorder. As a rule, hepatic invasion cases with complications associated with HCC require treatment with EVL. With this consideration in mind, the above remarks on safety suggest that, in most cases, EVL using a multi-band ligator should be the first modality selected. Provided that EVL using a multi-band ligator is performed or supervised by a skilled practitioner, we believe it can contribute to improving patient prognosis.

However, this method should only be performed in elective or prophylactic cases; EVL using a single-band ligator is preferable for emergency treatment, as in the case of active bleeding. In patients who are relatively young and with few comorbidities, EIS should be considered as a first-line treatment in the interests of achieving low recurrence rates.

28.5 Conclusions

This chapter describes how use of a multi-band EVL device can achieve accurate and safe ligation. However, this treatment can be dangerous if performed by a practitioner lacking sufficient experience. Where an expert in the treatment of variceal bleeding is unavailable, emergency endoscopy should be performed under general care and the source of the hemorrhage ascertained, using a Sengstaken-Blakemore tube or single-balloon occlusion to achieve temporary hemostasis. This procedure should be followed as soon as possible by the transfer of the patient to a specialized facility staffed by a well-trained endoscopist to treat variceal bleeding.

References

1. Fukui H, Saito H, Ueno Y, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51:629–50.
2. D'Amico G, Morabito A. Noninvasive markers of esophageal varices: another round, not the last. Hepatology. 2004;39:30–4.
3. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46:922–38.
4. Feu F, García-Pagán JC, Bosch J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet. 1995;346:1056–9.
5. D'Amico G, Garcia-Pagan JC, Luca A, et al. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. Gastroenterology. 2006;131:1611–24.
6. Burroughs AK, Triantos CK. Predicting failure to control bleeding and mortality in acute variceal bleeding. J Hepatol. 2008;48:185–8.
7. Ideo G, Bellati G, Fesce E, et al. Nadolol can prevent the first gastrointestinal bleeding in cirrhotics: a prospective, randomized study. Hepatology. 1988;8:6–9.
8. Garden OJ, Mills PR, Birnie GG, et al. Propranolol in the prevention of recurrent variceal hemorrhage in cirrhotic patients. A controlled trial. Gastroenterology. 1990;98:185–90.
9. Schepke M, Kleber G, Nurnberg D, et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. Hepatology. 2004;40:65–72.
10. Stiegmann GV, Goff JS, Michaletz Onody PA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med. 1992;326:1527–32.
11. Gimson AES, Ramage JK, Panos MZ, et al. Randomized trial of variceal banding ligation versus injection sclerotherapy for bleeding esophageal varices. Lancet. 1993;342:391–4.
12. Laine L, El-Newihi HM, Migikovsky B, et al. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. Ann Intern Med. 1993;119:1–7.
13. Hou MC, Lin HC, Kuo BIT, et al. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: a prospective randomized trial. Hepatology. 1995;21:1517–22.
14. Sarin SK, Govil A, Jain AK, et al. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. J Hepatol. 1997;26:826–32.
15. Baroncini D, Milandri GL, Borione D, et al. A prospective randomized trial of sclerotherapy versus ligation in the treatment of bleeding esophageal varices. Endoscopy. 1997;29:235–40.
16. Takeuchi M, Nakai Y, Sha S, et al. Combined ligation and paravariceal injection sclerotherapy for esophageal varices: outcome over 3 years. Gastroenterol Endosc. 1997;39:1189–95.
17. Jia Y, Dwivedi A, Elhanafi S, et al. Low risk of bacteremia after endoscopic variceal therapy for esophageal varices: a systematic review and meta-analysis. Endosc Int Open. 2015;03(05):409–17.

Chapter 29
Endoscopic Treatment of Esophageal Varices: Simultaneous Combination of Endoscopic Injection Sclerotherapy and Endoscopic Variceal Ligation

Tomoharu Yoshida, Yasuyuki Shirai, Koji Aoyama, and Tatsuya Noguchi

Abstract In combined therapy with endoscopic injection sclerotherapy and endoscopic variceal ligation (EISL), the two procedures are performed simultaneously. At our hospital, EISL is performed as the first-line treatment for elective and prophylactic cases of esophageal varices. In this chapter, we introduce the EISL technique and clinical results.

Keywords Endoscopic treatment · Esophageal varices · EISL · EVL · EIS

29.1 Introduction

In combined therapy with endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL) (EISL), the two procedures are performed simultaneously. EISL targets esophageal varices and was first reported by Nishikawa et al. [1] in 1995. EISL can be easily performed and is an effective treatment that involves EIS via intravascular injection of ethanolamine oleate (EO) and EVL via ligation of the puncture site. It is currently widely used in medical facilities [2–5]. At our hospital, EISL is performed as the first-line treatment method for elective and prophylactic cases of esophageal varices. In this chapter, we introduce the EISL technique and its procedures, focusing on treatment performance.

T. Yoshida (✉) · Y. Shirai · K. Aoyama · T. Noguchi
Department of Gastroenterology and Hepatology, Kokura Memorial Hospital, Kitakyushu, Fukuoka, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_29

29.2 EISL Procedure

Technique of EISL is introduced for elective and prophylactic cases of esophageal varices.

29.2.1 Instruments and Drugs Used

The instruments and drugs used are as follows:

- Pneumo-activated EVL device with cuff attachment (Sumitomo Bakelite Co. Tokyo, Japan)
- 23- or 25-G esophageal varix puncture needle (adjustable protrusion length type)
- Overtube
- 10% EO, contrast agent (1:1 solution of 5% EO)
- Dry sodium alginate powder
- Thrombin solution
- Alto Shooter
- Mouthpiece affixable with rubber band
- 20- and 2.5-mL injection syringe (Fig. 29.1)

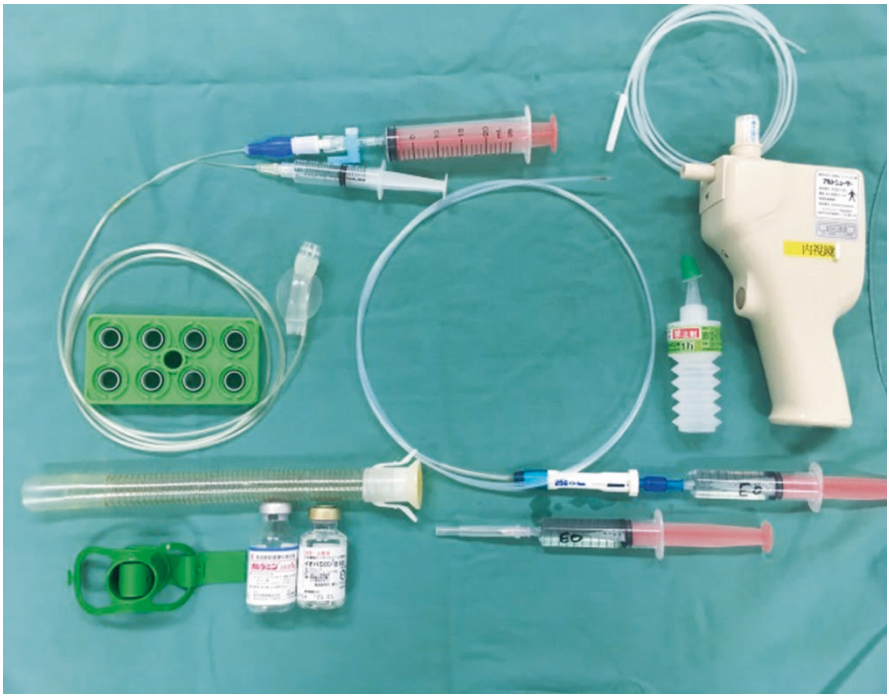


Fig. 29.1 Instruments and drugs used for EISL

29.2.2 Procedure

29.2.2.1 Pretreatment

To safeguard blood vessels, administer scopolamine butylbromide 20 mg or glucagon 1 mg intramuscularly to suppress peristalsis immediately prior to administering pentazocine 15 mg and hydroxyzine pamoate 25 mg via intramuscular injection.

In addition, while monitoring the patient, intravenously inject midazolam 2–5 mg and oxygen 2 L/min intranasally. Place the overtube beforehand to the scope and insert the scope.

29.2.2.2 Endoscopic Observations

Assess an appropriate puncture site based on endoscopic observations of the esophageal varices.

29.2.2.3 EISL Technique

Install the pneumo-activated EVL with a cuff to the scope (Figs. 29.2 and 29.3). Target the varix at the esophagogastric junction and position the biopsy channel of the scope toward the same direction as the target varix (7–8 o'clock angle).

29.2.2.4 EIS

Inflate the cuff with 15–20 cc of air and perform EIS. By using a 23- or 25-G puncture needle, adjust the protrusion length of the needle while considering the thickness and depth of the varices. Apply intermittent negative pressure to the syringe filled with EO with contrast medium (5% EO), and check for backflow of blood.

As the esophagus moves due to breathing, heartbeat, and peristaltic movements, it is important to keep the needle tip in the varices during EIS.

After confirmation of the puncture, slowly inject EO with contrast medium (5% EO) under fluoroscopy and into the left gastric vein that is a blood supply route for the varices. The maximum dose of 5% EO to be injected should be limited to 0.4 mL/kg per treatment session.

29.2.2.5 EVL

EVL is performed including at the puncture site, and the injection needle is removed.

After confirming the ligation site, remove the scope and install an O-ring again, and repeat the procedure for another varix. Lastly, apply thrombin and dry sodium alginate powder to the lower region of the esophagus. After this step, the first treatment is completed (Fig. 29.4).

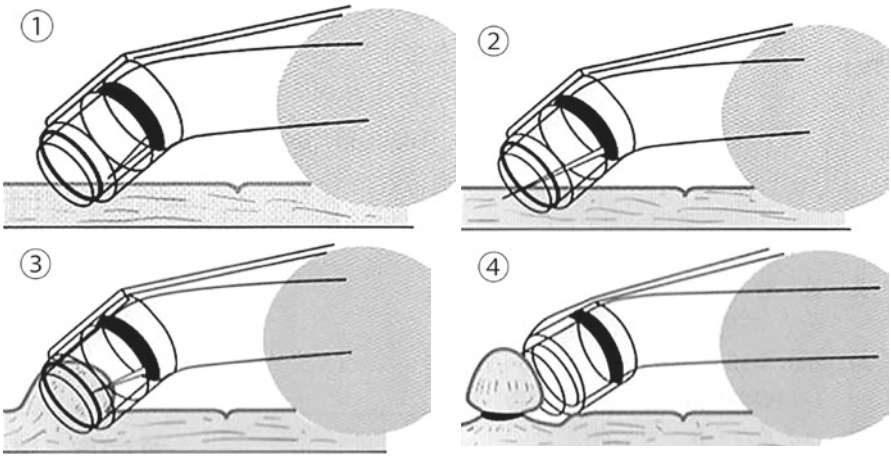


Fig. 29.2 Schematic diagram of EISL. Partially edited from Shigemitsu et al. [2]

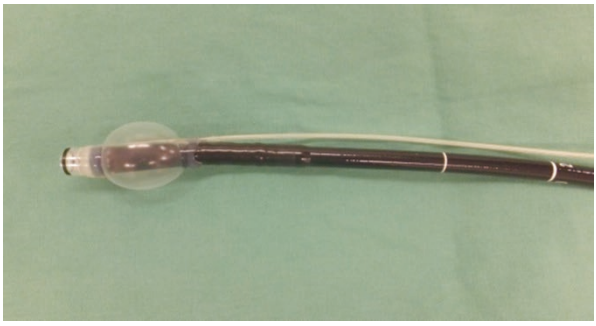


Fig. 29.3 Installation of the pneumo-activated EVL device with an endoscopically installed cuff

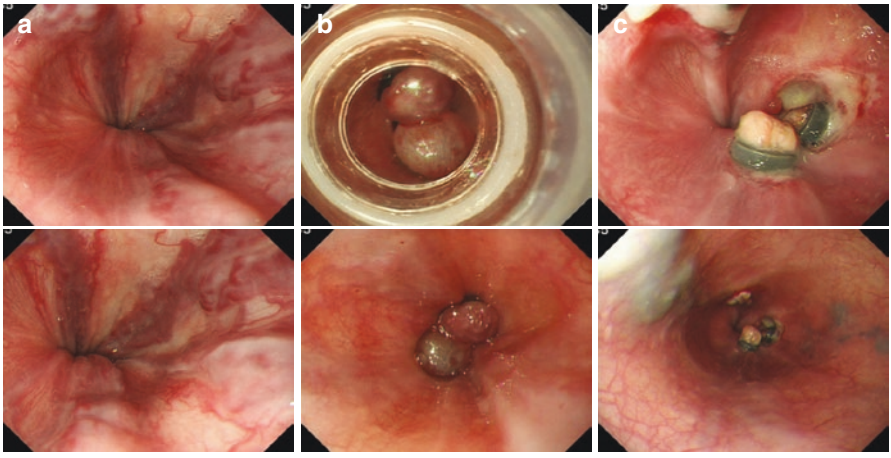


Fig. 29.4 Endoscopic images before and after EISL. (**a**) Before EISL, red color sign is observed. (**b**) Just after EISL. (**c**) One week after EISL, varices are thrombosed

29.3 Results and Complications

With regard to the recent cases involving esophageal varices treated by the authors, 103 were elective or prophylactic cases (elective, 35 cases; prophylactic, 68 cases). The average number of treatment sessions performed per case was 1.4 times, and the mean treatment time was approximately 15 min. Severe complication observed included perforation of the esophagus by the overtube (one case [1%], resolved through maintenance therapy). For cumulative recurrence rates, the 1-year recurrence rate was 12% and the 3-year recurrence rate was 27%.

For the recurrent cases after EISL, EISL was performed again followed by mucosal fibrosing using argon plasma coagulation (APC) to prevent further recurrence.

Nishikawa et al. [1] reported that EISL is effective because of interruption of blood flow and the absence of bleeding after removal of the needle.

Shigemitsu et al. [2] reported in the prospective randomized study that EISL is more useful for esophageal varices than EIS alone, and the cumulative relapse rate for 2 years was 18.5% for the EISL group.

29.4 Advantages of EISL

In comparison with EIS, the advantages of EISL include the following:

- Fewer treatment sessions
- Smaller amount of EO used
- Less time required for each treatment

29.5 Conclusion

EISL is a safe and useful treatment for esophageal varices.

References

1. Nishikawa Y, Hosokawa Y, Doi T, et al. Simultaneous combination of endoscopic sclerotherapy and endoscopic ligation for esophageal varices. Gastrointest Endosc. 1995;42:358–60.
2. Shigemitsu T, Yoshida T, Harada T, et al. Endoscopic injection sclerotherapy with ligation versus endoscopic injection sclerotherapy alone in the management of esophageal varices: a prospective randomized trial. Hepato-Gastroenterology. 2000;47:733–7.
3. Nishikawa Y, Hosokawa Y, Doi T, et al. Evaluation of endoscopic injection sclerotherapy with and without simultaneous ligation for the treatment of esophageal varices. J Gastroenterol. 1999;34:159–62.
4. Dhiman RK, Chawla YK. A new technique of combined endoscopic sclerotherapy and ligation for variceal bleeding. World J Gastroenterol. 2003;9:1090–3.
5. Miyaaki H, Ichikawa T, Taura N, et al. Endoscopic management of esophagogastric varices in Japan. Ann Transl Med. 2014;2:42.

Chapter 30
Endoscopic Treatment of Esophageal Varices: Combination of Endoscopic Variceal Ligation and Endoscopic Injection Sclerotherapy

Manabu Yamamoto and Hiroaki Suzuki

Abstract Endoscopic variceal ligation (EVL) was developed by Stiegmann et al. and has been performed using a device that allows aspiration and ligation of varices using rubber bands (O-rings). The advantage of this mechanical therapy rests on elimination of the need for injection of the sclerosant or tissue glues and, hence, obviation of many complications known to be associated with injection therapies. EVL was introduced to Japan by the authors in 1989, and thereafter, it became the first-line procedure especially for acute variceal bleeding.

On the other hand, in our initial experience of EVL in 1989, 20 out of 23 patients with esophageal varices showed an eradication effect as high as 86.9%; however, complete eradication (F_0) could only be observed in five patients (21.7%). To obtain better results, we then performed additional endoscopic injection sclerotherapy (EIS) using 1% polidocanol, which resulted in a 100% eradication effect with 43.5% complete eradication.

We perform EVL/EIS combined therapy for the prevention of variceal bleeding, and for acute bleeding cases, we have found EVL to be superior to other hemostatic options.

In this chapter, we introduce the historic aspect of EVL as well as our technical improvements including the development of an original device.

Keywords EVL · EIS · Polidocanol · Esophageal varices · Endoscopic treatment

M. Yamamoto (✉)
Adachi Kyosai Hospital, Tokyo, Japan
e-mail: fm3m-ymmt@asahi-net.or.jp

H. Suzuki
Department of Endoscopy, Jikei University School of Medicine, Tokyo, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_30

30.1 Introduction

Endoscopic variceal ligation (EVL) was developed by Stiegmann et al. [1] and has been performed using a device that allows aspiration and ligation of varices using rubber bands (O-rings). The advantage of this mechanical therapy rests on elimination of the need for injection of the sclerosant or tissue glues and, hence, obviation of many complications known to be associated with injection therapies. EVL was introduced to Japan by the authors in 1989 [2] and 150 patients with esophageal varices and 20 with gastric varices had been treated by March 1995 [3].

30.2 Results of the Previous Studies

In our initial experience of EVL in 1989, 20 out of 23 patients with esophageal varices showed an eradication effect as high as 86.9%. However, our endpoint of the therapy, complete eradication (F_0) [4], could only be observed in five patients (21.7%). To obtain better results, we then performed additional endoscopic injection sclerotherapy (EIS) using 1% polidocanol, and a 100% eradication effect (become F1 or F0 after the therapy) with 43.5% complete eradication was achieved [5]. The average volume of injected 1% polidocanol was 15 mL, which was less than a quarter of the dose used for patients who were treated by EIS alone. For three patients with active bleeding during this period, quick and secure hemostasis was achieved after a single ligation onto the bleeding point. There were no complications related to EVL alone or EVL with EIS.

30.3 Procedure of EVL/EIS Combined Therapy

30.3.1 Technique

Our first-line procedure for the treatment of esophageal varices is called EVL/EIS combined therapy where EVL is performed with ELS using 1% polidocanol in the same series of treatments. However, EVL without EIS [6–8] is still performed for patients with severe complications such as hepatic failure, renal failure, and disseminated intravascular coagulation (DIC).

EVL/EIS combined therapy is performed in a manner similar to conventional EIS in a sedated patient. An overtube that allows repeated endoscope insertion and withdrawal is attached to the endoscope before the survey endoscopic examination. After the survey examination of the upper gastrointestinal tract, the overtube is gently inserted, followed by withdrawal of the endoscope. The EVL device is then mounted and the loaded endoscope is reinserted through the overtube.

In patients bleeding from esophageal varices, a careful endoscopic examination is performed to find the bleeding point. If the bleeding point is found, direct ligation

(Fig. 30.1) onto the bleeding varix will be attempted [9]. In most of the cases, a single ligation is required to obtain complete hemostasis, but additional multiple ligations are recommended to supplement its efficacy. If the bleeding point cannot be found, EVL is started from slightly cephalad to the esophagogastric junction, and all varices are ligated with the spiral ligation method (Fig. 30.2) until the variceal blood flow has decreased and complete hemostasis can be obtained [10]. Additional EVL and/or EIS should be performed within a week after the initial treatment, and it should be repeated until complete eradication is achieved. For elective and

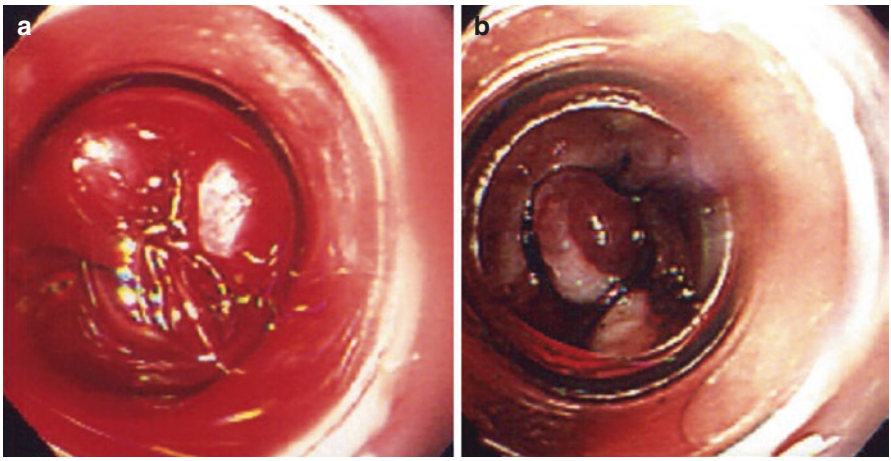


Fig. 30.1 If the bleeding point is found, place the device loaded endoscope directly onto the bleeding point and endoscopic ligation is performed. (**a**) Spurting bleeding was found through the EVL device. (**b**) Bleeding point was ligated and the complete hemostasis was obtained immediately

Fig. 30.2 If the bleeding point cannot be found, endoscopic ligation is started from slightly cephalad to the EG junction, and all varices are ligated with the spiral ligation method until the hemostatic effect is obtained

prophylactic patients, spiral ligations are performed initially. This method was developed to prevent unexpected esophageal strictures caused by healing of post-EVL ulcers [11]. In general, 2–3 individual ligations are attempted for each variceal channel up to a total of 8–12 ligations. A second session is held in a week after the initial treatment, and if there are varices larger than F_2, EVL is performed again. Such additional ligations should not be attempted near the post-EVL ulcer to prevent the severe bleeding by the ulcer tear. In our experience, additional ligation should be performed at least half an inch away from the post-EVL ulcer for the best prevention of bleeding. If the varices are smaller than F_1 or there is not enough space to add the safety ligation, EIS using 1% polidocanol is then performed. This is mainly attempted paravariceally on the distal esophagus to create the whole round ulcerations and reepithelialization of the esophageal wall. EIS is repeated every week until the complete eradication is achieved.

30.3.2 Outcomes of the Treatment

Overall outcome for 150 patients treated by EVL/EIS therapy showed 96% eradication which was as high as the eradication rate from our EIS trial (92%) [3]. From the viewpoint of the variceal form, 66 patients had F_3, 79 had F_2, and 5 had F_1 varices before the treatment. After a series of EVL/EIS therapy sessions, these statistics were improved to 6 patients with F_2, 67 with F_1, and 77 with F_0 (Fig. 30.3).

The details of the EVL/EIS therapy are as follows. EVL was performed for 180 sessions with an average of 1.2 sessions for each patient and 1530 ligations were attempted with 10.2 ligations per patient. Additional EIS was performed in a total of 285 sessions and the average number of sessions was 1.9 per patient. Altogether, 3800 mL of 1% polidocanol was injected and 25.3 mL was the average dose for each EVL/EIS session. This means the volume of injected sclerosant was decreased by a quarter from that used in EIS alone, and an average of 2.8 sessions were required to obtain the eradicating effect compared with 3.2 sessions for EIS alone. For the 17 patients who had active bleeding at the time of initial treatment, 10 direct ligations and 7 spiral ligations were performed, and 100% hemostasis was achieved [3].

There were five complications that required endoscopic treatment: two esophageal strictures (1.3%) and three post-therapeutic bleeding (2.0%). Strictures were

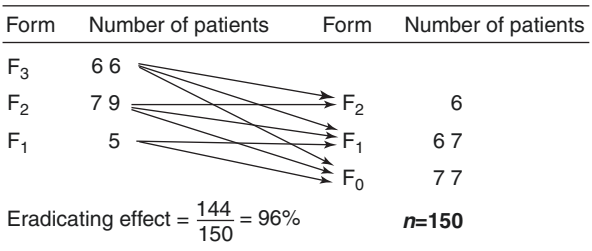


Fig. 30.3 Eradicating effect of EVL/EIS combined therapy ($n = 150$)

successfully treated by single or multiple endoscopic dilations and the bleeding was controlled by additional EIS. There were no deaths related to EVL/EIS therapy.

Recurrence of the varices was noted in 25 out of 41 patients (61%) who were followed up for more than 3 years. For such patients, additional endoscopic therapies were carried out mostly on an outpatient basis when recurrence was found. One or two sessions of low-volume EIS were required to obtain satisfactory results without any complications.

30.3.3 Improvement of the Device

EVL is very effective and easy to perform. However, we thought that the original device needed minor modifications to maximize the effectiveness of the therapy. Our problems with for the conventional device were as follows:

1. Visual field of the device attached to the endoscope is too narrow to observe the target varices and surroundings carefully.
2. Suction and/or irrigation to maintain a clear view during the treatment is limited since a trip wire occupies the endoscopic working channel.
3. The O-ring is not always released when ligation is performed in a retroflexed fashion.

To solve these problems, we first made a transparent EVL device with the cooperation of the original device manufacturer. This modification was fairly effective and the visual field of the endoscope became 70% more than the gray-colored device [12]. Then we also developed a new "pneumatic EVL device" to solve the other problems [13]. The pneumatic EVL device consists of a clear two-layer cylinder (an inner cylinder which the O-ring is stretched over and a sliding cylinder), air tube, and O-ring plate (Fig. 30.4). This device pushes the O-ring off with the sliding cylinder, which is activated by air injection, while the conventional device pulls a trip wire to move an inner cylinder toward the endoscope to release the O-ring. To load the device, the cylinder is first secured to the distal end of an endoscope followed by air tube taped over the endoscope. This allows us to keep the endoscopic working channel clear with suction and irrigation or to insert an injector needle for simultaneous EIS. By this mechanism, the O-ring can always be released even if the endoscope is fully retroflexed. Moreover, the O-ring plate eliminates complicated cylinder changing work and helps to prevent the transmission of blood-borne diseases to medical personnel. The O-ring plate has eight rubber bands and there is a preloading hole in the center of the plate to load and reload the O-rings smoothly. Prior to each O-ring loading, the device should be inserted to the preloading hole to push the sliding cylinder back to the working position. Then move the device onto the O-ring cylinder and push down vertically to complete the loading. From a questionnaire that we issued, it appeared that medical personnel appreciated this improvement very much more than we thought.

Insertion of an endoscopic overtube at the outset of the procedure facilitates withdrawal and reinsertion of the endoscope for multiple ligations and prevents unexpected aspiration of blood to the respiratory organs. However, complications related to the overtube insertion such as esophageal injury or perforations are reported [13]. To perform EVL more safely, we also developed the flexible overtube (Fig. 30.5) which is made of thinner silicon than the original one and reinforced by spiral wire like the esophageal prosthesis. The tip of a flexible tube is cut obliquely to prevent esophageal injury, and at the proximal end, anti-deflate film is placed to maintain a better visual field during the EVL. Unfortunately, the pneumatic EVL

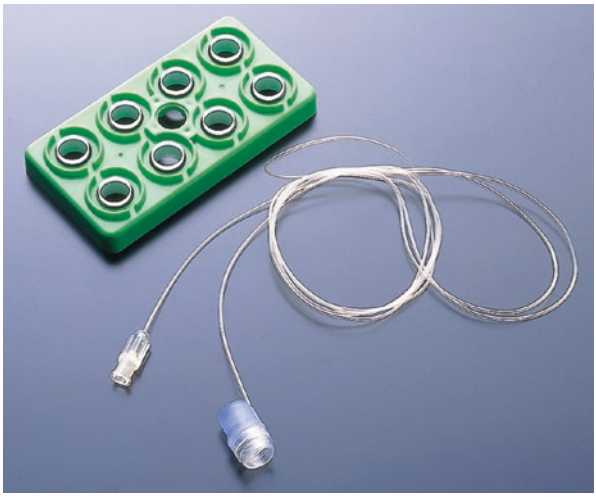


Fig. 30.4 The pneumatic EVL device consists of a friction fit clear cylinder, air tube, and syringe connector. The O-ring plate is equipped with eight rubber bands and a preloading hole in the center of the plate

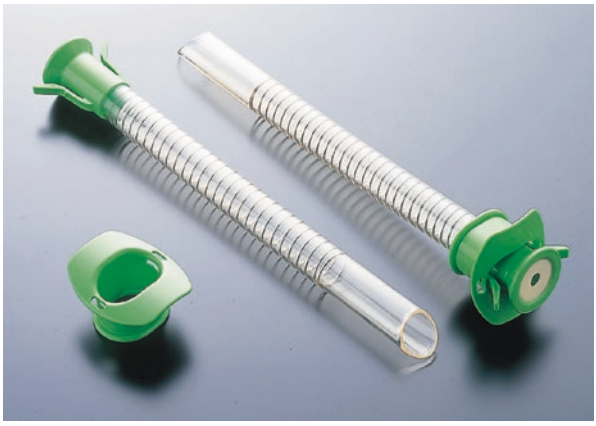


Fig. 30.5 The flexible overtube consists of a detachable mouthpiece and an overtube. The tip of the tube is obliquely cut and the soft silicon tube is reinforced by a spiral coil. Anti-deflate film is placed at the proximal end of the tube

device and the flexible overtube are currently available only in Japan due to patent issues, but we expect similar modifications will be made in each country to perform safer and easier EVL for patients suffering from variceal bleeding.

30.4 Discussion

The effects of EVL were examined experimentally using Jensen's portal hypertensive canine model by Stiegmann et al. [1]. Three to seven days following ligation of varices, slough of variceal tissue and shallow ulcerations were observed at all treatment sites. From 14 to 21 days after the treatment, there were minimal residual varices and no evidence of full-thickness esophageal injury. Sites where previously shallow ulcers had appeared were healed, and microscopic findings showed the full-thickness replacement of vascular structures in the submucosa with maturing scar tissue. An intense inflammatory response was present and reepithelialization of treated sites had occurred by the 21st day. The authors thought that the shallow ulcers produced at each ligated site resulted in little risk of bleeding and probably represented evidence of an effective treatment. Our follow-up animal study also paralleled to the results from their report [14].

Goff et al. [15] compared the patients who underwent EVL with those who underwent EIS and with untreated controls. They all had esophageal varices. Patients treated with EIS had a greater incidence of stricture formation, but esophageal manometric studies did not show persistent long-term differences among those three groups.

EVL was examined in both uncontrolled and prospective randomized studies and compared with EIS [3, 16–20]. Goff et al. [18] studied 146 consecutive nonselected patients with variceal hemorrhage who were treated by EVL for control of acute hemorrhage and were then serially treated to achieve variceal eradication. Control of active variceal hemorrhage was accomplished in 94% of 33 patients who were actively bleeding at the time of index endoscopy. Variceal obliteration was achieved in 79% of the 125 patients who remained in the trial for more than 30 days with a mean of 5.5 endoscopic treatment sessions. Recurrent hemorrhage occurred in 44% and the overall survival rate in 146 patients who entered the study was 73% at a mean follow-up of 15 months. A total of four treatment-related non-bleeding complications were observed. Data from prospective randomized trials [19, 20] support the contention that EVL is at least as effective as EIS for prevention of recurrent hemorrhage and resulted in comparable survival while inflicting a minimum risk of non-bleeding complications.

Reveille et al. [21] combined EVL with low-volume EIS and reported that combination therapy may theoretically result in more rapid variceal obliteration because of the additive effects of mechanical stasis by EVL and intimal damage by EIS. Their experience consisted of 46 patients and eradication was accomplished in 76% of

patients with a mean of 3.1 treatment sessions. The rebleeding rate was 30% with one death resulting from hemorrhage. Overall survival at 6 months was 85%. These data support the contention that the more rapid eradication may be possible with combined EVL/EIS. They concluded that further confirmation of these data is needed before solid conclusions can be drawn, and we confirmed in our uncontrolled trial that the combination therapy is superior to EVL alone [3].

30.5 Conclusion

Endoscopic treatment for esophageal varices is already an accomplished procedure, but we should be trying to improve the technique and/or develop a new procedure to obtain better results. We consider that the most important issue for the management of esophageal varices is having as many therapeutic options as we can and selecting the best therapy for each patient.

References

1. Stiegmann GV, Sun JH, Hammond WS. Results of experimental endoscopic esophageal varix ligation. Ann Surg. 1988;54:105.
2. Yamamoto M, Suzuki H, Aoki T, et al. Endoscopic variceal ligation (in Japanese). Endosc Dig. 1990;2:269.
3. Yamamoto M, Suzuki H. Efficacy of endoscopic variceal ligation for esophageal varices (in Japanese). Surgery. 1995;57:657.
4. The Japan Society for Portal Hypertension. The general rules for study of portal hypertension (in Japanese). 3rd ed. Tokyo: Kanehara & Co., Ltd.; 2013.
5. Ohnishi T, Yamamoto M, Aoki T, et al. Combination of endoscopic variceal legation and endoscopic sclerotherapy with 1% polidocanol: effect on esophageal varices (in Japanese). Prog Dig Endosc. 1991;39:157.
6. Stiegmann GV, Yamamoto M, Goff JS, Reveille RM. Technique and current results of endoscopic of variceal ligation. Prog Dig Endosc. 1991;39:11.
7. Stiegmann GV, Yamamoto M. Approaches to the endoscopic treatment of esophageal varices. World J Surg. 1992;16:1034.
8. Yamamoto M, Stiegmann GV. Current status of band ligation for esophageal varices. Probl Gen Surg. 1992;9:477.
9. Stiegmann GV, Yamamoto M. Endoscopic techniques for the management of active variceal bleeding. Gastrointest Endosc Clin N Am. 1992;2:59.
10. Yamamoto M, Suzuki H. Technique and current results of endoscopic variceal ligation (in Japanese). Rinsho Geka. 1994;49:411.
11. Yamamoto M. Endoscopic variceal ligation. Phys J. 1992;1:66.
12. Yamamoto M, Suzuki H. A technical commentary: endoscopic variceal ligation (in Japanese). Clin Gastroenterol. 1995;10:161.
13. Yamamoto M, Suzuki H. Endoscopic variceal ligation: is the procedure really safe, easy and effective (in Japanese). Endosc Dig. 1995;7:19.
14. Yamamoto M, Suzuki H. Endoscopic injection sclerotherapy for esophageal varices (in Japanese). Tokyo: Endoscopic Variceal Ligation; 1992. p. 201–8.

15. Goff JS, Reveille RM, Stiegmann GV. Endoscopic sclerotherapy versus endoscopic variceal ligation: esophageal symptoms, complications and motility. Am J Gastroenterol. 1988;83:1240.
16. Hall RJ, Lilly JR, Stiegmann GV. Endoscopic esophageal varix ligation: technique and preliminary results in children. J Pediatr Surg. 1988;23:1222.
17. Saeed Z, Michaletz P, Winchester C, et al. Endoscopic variceal ligation in patients who have failed sclerotherapy. Gastrointest Endosc. 1990;36:572–4.
18. Goff JS, Reveille RM, Sun JH, Stiegmann GV. Three years experience with endoscopic variceal ligation (EVL) for treatment of bleeding varices. Endoscopy. 1992;24:401.
19. Stiegmann GV, Goff JS, Michaletz-Onody PA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med. 1992;326:1527.
20. El-Newihi H, Migicovsky B, Laine L. A prospective randomized comparison of sclerotherapy and ligation for the treatment of bleeding esophageal varices (abstract). Gastroenterology. 1991;100:A59.
21. Reveille RM, Goff JS, Stiegmann GV, Stauffer JT. Combination endoscopic variceal ligation (EVL) and low volume sclerotherapy (ES) for bleeding esophageal varices: a faster route to variceal eradication (abstract). Gastrointest Endosc. 1991;37:243.

Chapter 31
Endoscopic Treatment of Esophageal Varices: Endoscopic Variceal Ligation Followed by Argon Plasma Coagulation

Shinichi Nakamura

Abstract The endoscopic approach is currently the preferred choice for treatment of esophageal varices, with endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL) both being widely performed. Several clinical trials have compared the combination of EVL and EIS with EVL alone or with EIS alone. Esophageal varices tend to recur more often after EVL than EIS, and therefore additional treatment is warranted with the former procedure. To prevent recurrence, it is not only essential to completely eliminate the varices but also to produce fibrosis of esophageal mucosa. Argon plasma coagulation (APC) is a noncontact coagulation method that involves the application of a high-frequency electrical arc to a jet of argon gas. APC allows shallow coagulation of an extensive area within a short period of time, making it ideal for mucosal fibrosis therapy of esophageal varices. EVL combined with APC is superior to EVL alone and is not associated with major complications. Since APC is theoretically well suited for mucosal fibrosis therapy, it can be used for complete elimination of esophageal varices and for fibrosis of the distal esophageal mucosa.

Keywords Argon plasma coagulation (APC) · Endoscopic variceal ligation (EVL) · Esophageal varices · Therapeutic endoscopy

31.1 Introduction

Esophagogastric varices are one of the manifestations of portal hypertension associated with liver cirrhosis. Esophagogastric varices can be managed by endoscopic treatment, interventional radiology techniques, or surgery, but the main approach at

S. Nakamura (✉)
Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan
e-mail: shinichi.ige@twmu.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_31

present is endoscopic therapy such as endoscopic injection sclerotherapy (EIS) [1, 2] and endoscopic variceal ligation (EVL).

EVL was introduced clinically by Stiegmann et al. [3–5] in 1988 and rapidly adopted because it is a simple procedure not associated with any risk of bleeding from a puncture site in the varices or adverse reactions like those encountered with injection of a sclerosing agent. The introduction of EVL has allowed the implementation of prophylactic treatment and also simplified hemostasis in patients with bleeding varices. While treatment of esophageal varices is not a field limited to specialists, it is important to revise the regulations continuously and provide adequate training for physicians interested in specializing in endoscopy.

Several clinical trials have compared the combination of EVL and EIS with EVL alone, or with EIS alone. Esophageal varices tend to recur more often after EVL compared with EIS, and therefore additional treatment is warranted with the former procedure. To prevent recurrence, it is not only essential to completely eliminate the varices but also to produce fibrosis of esophageal mucosa. In fact, previous studies have demonstrated that therapy that promotes mucosal fibrosis is often useful. Perivariceal injection sclerotherapy with 1% polidocanol is typically used to supplement EVL, though other methods have also been used such as thermal coagulation by laser or high-frequency electric current [6–12].

31.2 Clinical Outline of Argon Plasma Coagulation

Argon plasma coagulation (APC) is a noncontact coagulation method that involves the application of a high-frequency electrical arc to a jet of argon gas. APC is already employed during laparotomy and laparoscopic surgery, and Grund et al. [13, 14] have developed APC equipment that can be used with an endoscope. APC allows easy control of the depth of coagulation, thus allowing simpler shallow tissue coagulation compared with monopolar electrocoagulation or laser coagulation [15, 16]. APC is also reported to be useful for hemostasis of bleeding ulcers [17–19], for angioectasia [20, 21] and radiation enteritis [22], and for coagulation of Barrett's epithelium [23] and malignant tumors [24, 25]. The distinguishing characteristic of APC is that shallow coagulation can be achieved over an extensive area within a short period of time, making it ideal for mucosal fibrosis therapy of esophageal varices.

31.3 Technique of EVL Plus APC Method

Variceal ligation can be achieved using a GIF-Q290 electronic endoscope (Olympus Co., Tokyo, Japan) with a pneumo-activated EVL device (Sumitomo Bakelite Co. Ltd., Tokyo, Japan) or Speedband Superview Super 7 (Boston Scientific, Natick, MA, USA). APC is performed with a high-frequency generator (Erbotom ICC 200),

an automatically regulated argon source (Argon Beamer Two order APC 300), and flexible APC probes (all manufactured by ERBE Elektromedizin, Tübingen, Germany). Recently, a high-frequency generator (VIO200D), argon source (APC2), and FiAPC probe (all manufactured by ERBE Electoromedizin, Tubingen, Germany) have been used. Before treatment, patients are asked to drink 60 mL of a solution containing an antifoaming agent and mucolytic agent for mucus clearance from the distal esophagus. Lidocaine spray is used to induce topical anesthesia of the pharynx, and a relaxant as well as intravenous sedation are administered if required. With the aim of preventing/stopping of bleeding and protecting the wound after completion of treatment, sodium alginate solution and thrombin granules are administered orally, and meals consisting of rice gruel are started from the day following the procedure [26].

For EVL, sedation is provided and an overtube is used when required. EVL involves ligation of the esophageal varices from immediately above the esophagogastric junction (EGJ). The procedure is continued until the varix shrinks to F1 level without red color sign or smaller. This is followed by mucosal fibrosis therapy using APC. The residual mucosa including all trivial varices is coagulated completely by APC. During the conduct of APC, a transparent hood is fitted to the tip of the endoscope. APC is performed using argon gas at a flow rate of 1.5 L/min and a high-frequency arc output of 50 W. The recent equipment of VIO200D-APC2 is used set at coagulation mode of Forced or Pulsed. Tissue coagulation is performed in the distal esophagus from the EGJ to 5 cm proximally (Figs. 31.1 and 31.2). APC is repeated every week with a 1-week interval between treatment sessions, and treatment is terminated after complete eradication of the varices is confirmed. Patients are followed up by endoscopy every 3 or 6 months for early detection of any variceal recurrence.

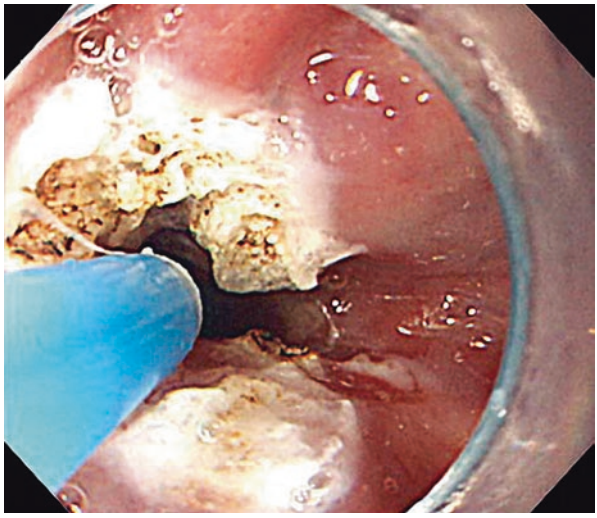


Fig. 31.1 Endoscopic view of the distal esophagus. Tissue coagulation could be achieved after the initial APC session

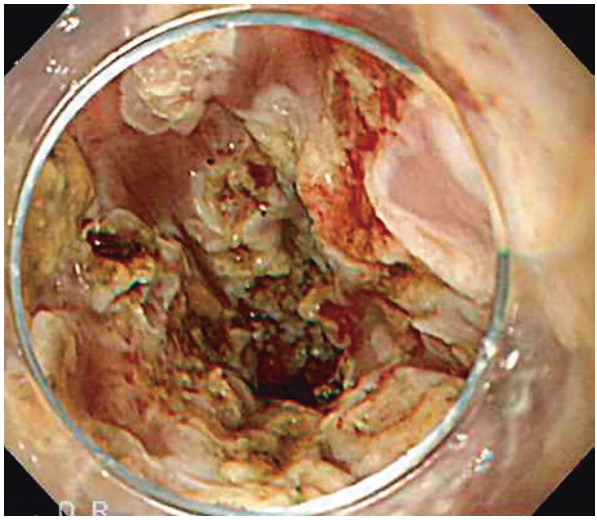


Fig. 31.2 Endoscopic view of the distal esophagus. Esophageal mucosa 4–5 cm proximal to the EGJ was thermocoagulated circumferentially with APC

31.4 Results

Nakamura et al. [26] used APC to induce mucosal fibrosis and compared the efficacy of EVL plus APC with EVL alone in the treatment of esophageal varices. Their prospective study included 30 patients with esophageal varices randomly assigned to receive APC after EVL (combination group) and 30 patients who received EVL only (ligation group) and involved comparison of the treatment outcomes and complications. The mean (±SD) follow-up period was 18.5 ± 6.8 and 15.8 ± 7.7 months for the combination and ligation groups, respectively. The cumulative recurrence-free rate at 24 months after treatment for the combination group was significantly higher than that in the ligation group (74.2% vs. 49.6%, $p < 0.05$). Furthermore, a significantly higher incidence of pyrexia was encountered in the combination group ($p < 0.05$), but the incidences of other complications were similar in the two groups. They concluded that EVL plus APC is superior to EVL alone.

Furukawa et al. [27] also evaluated the clinical usefulness and safety of APC. Their study included 11 patients with imminent signs of esophageal variceal bleeding. Before APC, these patients underwent EVL with consequent improvement of esophageal varices from F3 (large) to disappearance or F1 (small). All patients were followed up for a mean posttreatment period of 637.4 ± 56.5 days, and no obvious recurrence of varices in the so-called critical area was noted. They concluded that APC was an effective prevention consolidation therapy after EVL without serious complications. During the course of the study, no serious complications were noted. After APC, transient fever occurred in 13 patients and 8 complained of dysphagia or retrosternal pain/discomfort. The mean follow-up for all patients was 16 months (range 9–28 months). No recurrence of varices or variceal hemorrhage was observed in the APC group, whereas varices recurred in 42.8% (6/14) of the patients of the control group ($p < 0.04$) and bleeding recurred in 7.2% (1/14).

Cipolletta et al. [28] investigated whether APC was effective in reducing variceal recurrence after EVL. In the APC group, the entire esophageal mucosa 4–5 cm proximal to the EGJ was thermocoagulated circumferentially with APC in one to three sessions performed at weekly intervals. Subsequently, endoscopy was performed every 3 months to check for recurrence of varices in both groups. During the course of the study, no serious complication was noted. After APC, transient fever occurred in 13 patients and 8 complained of dysphagia or retrosternal pain/discomfort. The mean follow-up for all patients was 16 months (range 9–28 months). No recurrence of varices or variceal hemorrhage was observed in the APC group, whereas varices recurred in 42.8% (6/14) of patients of the control group ($p < 0.04$) and bleeding recurred in 7.2% (1/14). They concluded that APC of the distal esophageal mucosa after eradication of esophageal varices by EVL was safe and effective in reducing the rate of variceal recurrence.

In a recent article in this field, Kondo et al. [29] examined the effects of EIS with APC as the primary/secondary prophylaxis for esophageal varices on portal hemodynamics and long-term outcome in cirrhosis. Their prospective study included 48 cirrhotic patients (age, 64.5 ± 11.4 years; 26 bleeders, 22 non-bleeders). Posttreatment outcome (EIS and APC; median observation period, 12.8 months for recurrence and 21.1 months for prognosis) was evaluated with respect to the findings of hepatic venous catheterization, Doppler ultrasound, and endoscopic ultrasonography. Cumulative variceal recurrence/rebleeding rates were 25.5%/5.6% and 62.4%/23.1% at 1 and 3 years, respectively. The cumulative overall survival rates were 95.2% and 71.9% at 1 and 3 years, respectively, showing no significant relationship with hepatic venous pressure gradient. They concluded that EIS with APC for esophageal varices was unlikely to have a significant effect on portal pressure.

In conclusion, APC is theoretically well suited for mucosal fibrosis therapy; it can be used for complete elimination of esophageal varices and for fibrosis of the distal esophageal mucosa. APC appears to be effective for improving the therapeutic results in the treatment of esophageal varices.

References

1. Kitano S, Koyanagi N, Iso Y, Higashi H, Sugimachi K. Prevention of recurrence of esophageal varices after endoscopic injection sclerotherapy with ethanolamine oleate. Hepatology. 1987;7:810–5.
2. Infante-Rivard C, Esnaola S, Villeneuve JP. Role of endoscopic variceal sclerotherapy in the long-term management of variceal bleeding: a meta-analysis. Gastroenterology. 1989;96:1087–92.
3. Stiegmann GV, Goff JS. Endoscopic esophageal varix ligation: preliminary clinical experience. Gastrointest Endosc. 1988;34:113–7.
4. Stiegmann GV, Sun JH, Hammond WS. Results of experimental endoscopic esophageal varix ligation. Am Surg. 1988;54:105–8.
5. Stiegmann GV, Goff JS, Michaletz-Onody PA, Korula J, Liebeman D, Saeed ZA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med. 1992;326:1527–32.

6. Gimson AES, Ramage JK, Panos MZ, Hayllar PM, Williams R, Westaby D. Randomized trial of variceal banding ligation versus injection sclerotherapy for bleeding oesophageal varices. Lancet. 1993;342:391–4.
7. Laine L, El-Newihi HM, Migikovsky B, Sloane R, Garcia F. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. Ann Intern Med. 1993;119:1–7.
8. Hou MC, Lin HC, Kuo BI, Chen CH, Lee FY, Lee SD. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: a prospective randomized trial. Hepatology. 1995;21:1517–22.
9. Lo GH, Lai KH, Cheng JS, Hwu JH, Chang CF, Chen SM, et al. A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. Hepatology. 1995;22:466–71.
10. Saeed ZA, Stiegmann GV, Ramirez FC, Reveille RM, Goff JS, Hepps KS, et al. Endoscopic variceal ligation is superior to combined ligation and sclerotherapy for esophageal varices: a multicenter prospective randomized trial. Hepatology. 1997;25:71–4.
11. Baroncini D, Milandri GL, Borioni D, Piemontese A, Cennamo V, Billi P, et al. A prospective randomized trial of sclerotherapy versus ligation in the elective treatment of bleeding esophageal varices. Endoscopy. 1997;29:235–40.
12. Imperiale TF, Chalasani N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding. Hepatology. 2001;33:802–7.
13. Grund KE, Storek D, Farin G. Endoscopic argon plasma coagulation (APC): first clinical experiences in flexible endoscopy. Endosc Surg. 1994;2:42–6.
14. Grund KE, Zindel C, Farin G. Argon Plasma Koagulation in der flexiblen Endoscopie. Bewertung eines neuen therapeutischen Verfahrens nach 1606 Anwendungen. Dtsch Med Wochenschr. 1997;122:432–8.
15. Wahab PJ, Mulder CJJ, den Hartog G, Thies JE. Argon plasma coagulation in flexible gastrointestinal endoscopy: pilot experiences. Endoscopy. 1997;29:176–81.
16. Watson JP, Bennett MK, Griffin SM, Mattewson K. The tissue effect of argon plasma coagulation on esophageal and gastric mucosa. Gastrointest Endosc. 2000;52:342–5.
17. Cipolletta L, Bianco MA, Rotondano G, Piscopo R, Prisco A, Garofano ML. Prospective comparison of argon plasma coagulator and heater probe in the endoscopic treatment of major peptic ulcer bleeding. Gastrointest Endosc. 1998;48:191–5.
18. Chau CH, Siu WT, Law BKB, Tang CN, Kwok SY, Luk YW, et al. Randomized controlled trial comparing epinephrine injection plus heat probe coagulation versus epinephrine injection plus argon plasma coagulation for bleeding peptic ulcers. Gastrointest Endosc. 2003;57:455–61.
19. Komatsu H, Hara Y, Naito Y, Hosaka Y, Yamanaka S, Masuda H, et al. Effect of argon plasma coagulation in patients with upper gastrointestinal active hemorrhage. Dig Endosc. 2005;17:13–6.
20. Kitamura T, Tanabe S, Koizumi W, Ohida M, Saigenji K, Mitomi H. Rendu-Osler-Weber disease successfully treated by argon plasma coagulation. Gastrointest Endosc. 2001;54:525–7.
21. Olmos JA, Marcolongo M, Pogorelsky V, Varela E, Davolos JR. Argon plasma coagulation for prevention of recurrent bleeding from GI angiodysplasias. Gastrointest Endosc. 2004;60:881–6.
22. Kaassis M, Oberti E, Burtin P, Boyer J. Argon plasma coagulation for the treatment of hemorrhagic radiation proctitis. Endoscopy. 2000;32:673–6.
23. Van Laethem JL, Jagodzinski R, Peny MO, Cremer M, Deviere J. Argon plasma coagulation in the treatment of Barrett's high-grade dysplasia and in situ adenocarcinoma. Endoscopy. 2001;33:257–61.
24. Akhtar K, Byrne JP, Bancewicz J, Attwood SE. Argon beam plasma coagulation in the management of cancers of the esophagus and stomach. Surg Endosc. 2000;14:1127–30.
25. Sagawa T, Takayama T, Oku T, Hyashi T, Ota H, Okamoto T, et al. Argon plasma coagulation for successful treatment of early gastric cancer with intramucosal invasion. Gut. 2003;52:334–9.

26. Nakamura S, Mitsunaga A, Murata Y, Suzuki S, Hayashi N. Endoscopic induction of mucosal fibrosis by argon plasma coagulation (APC) for esophageal varices: a prospective randomized trial of ligation plus APC vs. ligation alone. Endoscopy. 2001;33:210–5.
27. Furukawa K, Aoyagi Y, Harada T, Enomoto H. The usefulness of prevention consolidation therapy of esophageal varices using argon plasma coagulation technique. Hepatol Res. 2002;23:220–5.
28. Cipolletta L, Bianco MA, Rotondano G, Marmo R, Meucci C, Piscopo R. Argon plasma coagulation prevents variceal recurrence after band ligation of esophageal varices: preliminary results of a prospective randomized trial. Gastrointest Endosc. 2002;56:467–71.
29. Kondo T, Maruyama H, Kiyono S, Sekimoto T, Shimada T, Takahashi M, et al. Eradication of esophageal varices by sclerotherapy combined with argon plasma coagulation: effect of portal hemodynamics and longitudinal clinical course. Dig Endosc. 2016;28:152–61. https://doi.org/10.1111/den.12562.

Chapter 32
Endoscopic Treatment of Esophageal Varices: Simultaneous Combination of Endoscopic Injection Sclerotherapy and Endoscopic Variceal Ligation for Prevention of Recurrence

Fumio Chikamori

Abstract The Takase method of endoscopic injection sclerotherapy (EIS) obliterates esophagogastric varices and their associated blood supply. Obliteration of blood supply routes contributes to lower the recurrence of esophageal varices after EIS. In endoscopic injection sclerotherapy with simultaneous ligation (EISL), EIS is performed first followed by endoscopic variceal ligation (EVL). The suction of the injection site is maintained after EIS to facilitate EVL. Band ligation is performed at the site of injection. As the blood flow is blocked by ligation, EISL allows the sclerosant to remain at the site. It is less invasive and requires fewer sessions and less sclerosant. There is less chance of bleeding from the injection site as the variceal puncture is ligated. EISL is indicated for esophageal varices, especially for pipeline varices, cardiac varices which drain into esophageal varices, and/or special type of varices.

Keywords Endoscopic injection sclerotherapy with simultaneous ligation · Esophagogastric varices · Endoscopic injection sclerotherapy · Endoscopic variceal ligation

32.1 Introduction

The Takase method of endoscopic injection sclerotherapy (EIS) obliterates esophagogastric varices and their associated blood supply [1]. Obliteration of blood supply routes contributes to lower the recurrence of esophageal varices after EIS [2]. Endoscopic variceal ligation (EVL) [3] is a noninvasive method, in which esophageal varices are ligated mechanically. It is thought that it has fewer complications than EIS. It can be used in patients with or without portal hypertension. It holds the

F. Chikamori (✉)
Department of Surgery, Tano Hospital, Kochi, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_32

part or whole of a varix resulting in occlusion and thrombosis. The tissue necroses and sloughs off in few days to weeks. However, EVL does not obliterate the variceal feeder causing high rate of recurrence. Nishikawa et al. [4, 5] reported a further progression in the treatment of esophageal varices and described EIS with simultaneous variceal ligation (EISL). It is expected to give a synergistic effect of both EIS and EVL.

32.2 Technical Aspects, Merits, and Indication

32.2.1 Technical Aspects

EISL is based upon the Takase method of EIS combined with EVL. In EISL, EIS is performed first followed by EVL. The suction of the injection site is maintained after EIS to facilitate EVL. Band ligation is performed at the site of injection.

32.2.2 Merits and Indication

It is less invasive and requires fewer sessions and less sclerosant. There is less chance of bleeding from the injection site as the variceal puncture is ligated. The effectiveness of EIS depends on the time that the sclerosant remains in contact with endothelium promoting inflammation leading to venous thrombosis and embolization. As the blood flow is blocked by ligation, EISL allows the sclerosant to remain at the site. Nishikawa et al. [5] reported that the mean number of treatment sessions required for eradication of esophageal varices was 2.3 ± 0.5 for EISL and 3.9 ± 0.8 for EIS ($p < 0.01$); the mean number of treatment sites was 6.2 ± 2.2 for EISL and 14.0 ± 5.0 for EIS ($p < 0.001$); the mean total amount of EOI used was 13.8 ± 5.2 mL for EISL and 26.3 ± 9.8 mL for EIS ($p < 0.01$). Shigemitsu et al. [6] reported that the red color sign disappeared in 83% (10/12) in the EISL group and 25% (3/12) in the EIS group ($p < 0.01$). Umehara et al. [7] reported that the 1- and 3-year cumulative recurrence rates in the EISL group (9.5%, 22.1%) were significantly lower than those in the EVL group (61.9%, 72.2%) ($p < 0.01$). EISL is indicated for esophageal varices, especially for pipeline varices, cardiac varices which drained to esophageal varices, and/or special type of varices [8].

32.3 Case Report

A 57-year-old female with extrahepatic portal obstruction was admitted for the treatment of esophagogastric varices (Figs. 32.1a, b and 32.2a). She had a previous history of simple esophageal transection and splenectomy. The Child-Pugh score

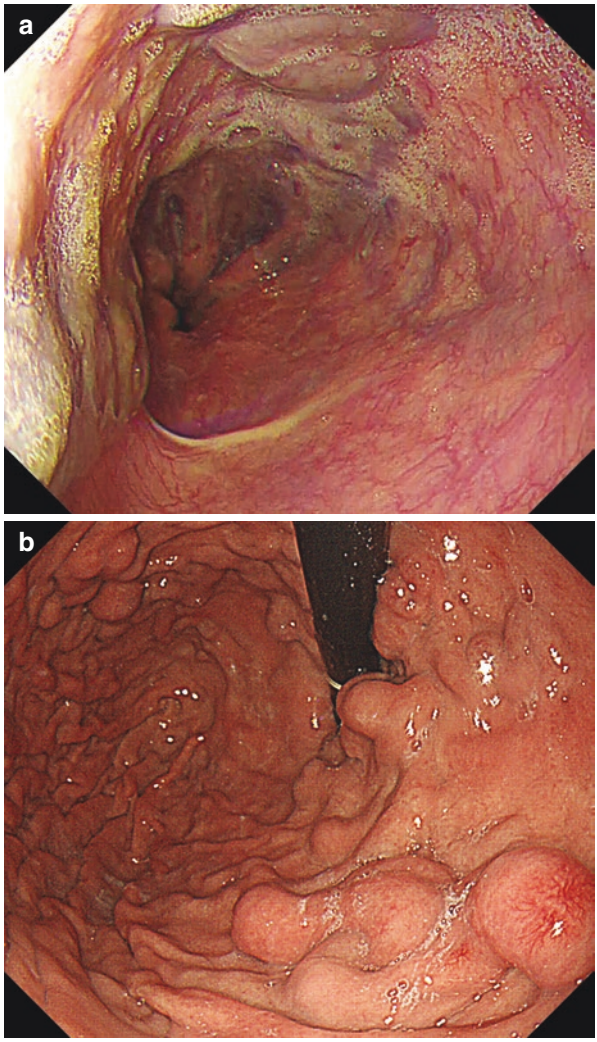


Fig. 32.1 (**a**) Endoscopic picture showing esophageal varices and scar of esophageal transection. (**b**) Endoscopic picture showing gastric varices located at the cardia and fundus

was grade A. Antibodies to hepatitis B and C were negative. This case was treated by left gastric arterial embolization (LGE), transileocolic vein obliteration (TIO), and EISL. Celiac arteriography showed that the left gastric artery (LGA) was not affected by previous esophageal transection, so embolization of LGA was firstly performed (Fig. 32.3a). Superior mesenteric arterioportography showed that portal vein was obstructed and the esophagogastric varices were supplied by the cavernous transformation (Fig. 32.3b). Under general anesthesia, TIO was performed. The blood supply route of esophagogastric varices was branched from the left hepatic side cavernous transformation (Fig. 32.3c). This supply route was embolized using microcoils, 2.5 mL of ethanol, and 12 mL of 50% glucose. Portal venous pressure was changed from 28 to 32 cmH_2O by TIO (Fig. 32.3d). Two days after TIO, EISL

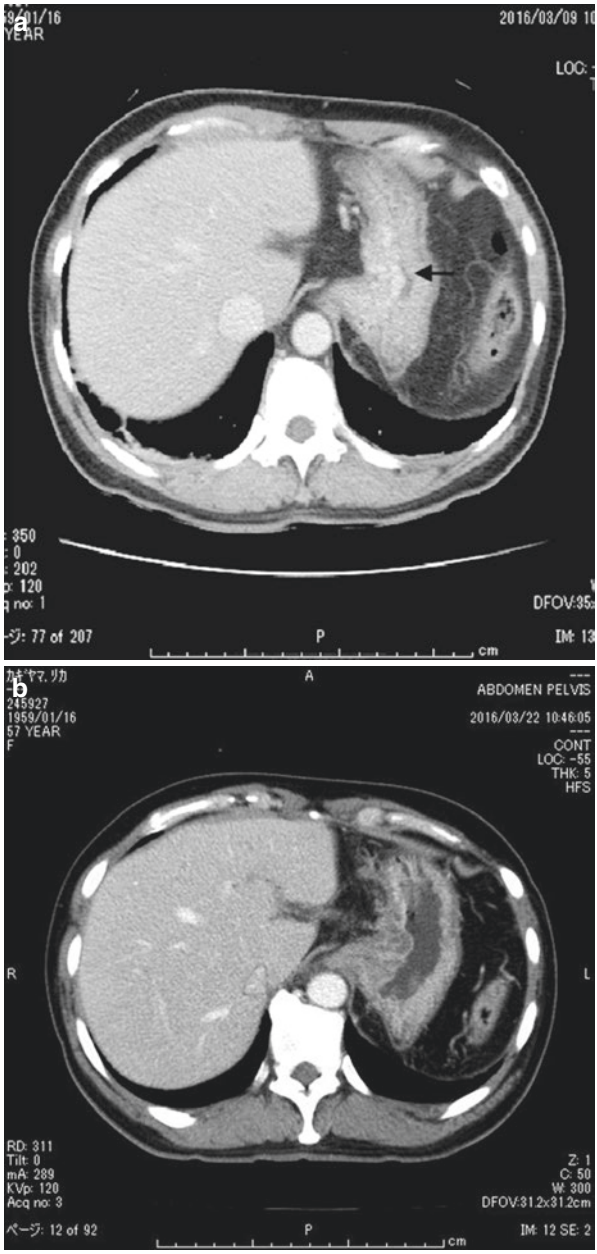


Fig. 32.2 (**a**) CT showing gastric varices (arrow). (**b**) CT 1 week after EISL showing obliteration of gastric varices with thrombi

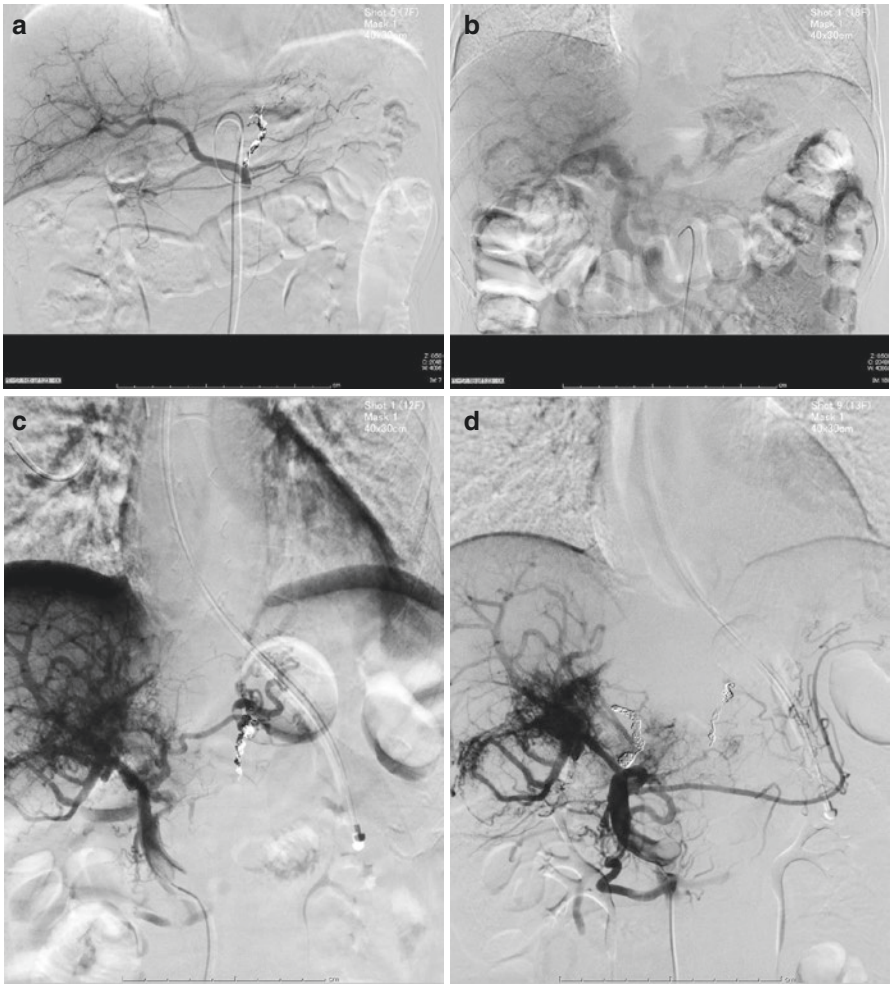


Fig. 32.3 (**a**) Celiac arteriogram showing the embolization of LGA using microcoils. (**b**) Superior mesenteric arterioportogram showing that portal vein is obstructed and the esophagogastric varices are supplied by the cavernous transformation. (**c**) Transileocolic venogram showing that the blood supply route of esophagogastric varies is branched from the left hepatic side cavernous transformation. (**d**) Transileocolic venogram showing the embolization of supply route

was performed. At total of 20 mL of 5% EOI was injected intermittently over a period of 12 min. Endoscopic varicography revealed cardiac venous plexus clearly (Fig. 32.4). After that, endoscopic variceal ligations were performed at 12 points. CT was conducted a week after EISL revealed that the esophagogastric varices had been completely obliterated by thrombi (Fig. 32.2b). Endoscopy 1 month after EISL proved the esophagogastric varices had been eradicated (Fig. 32.5a, b).

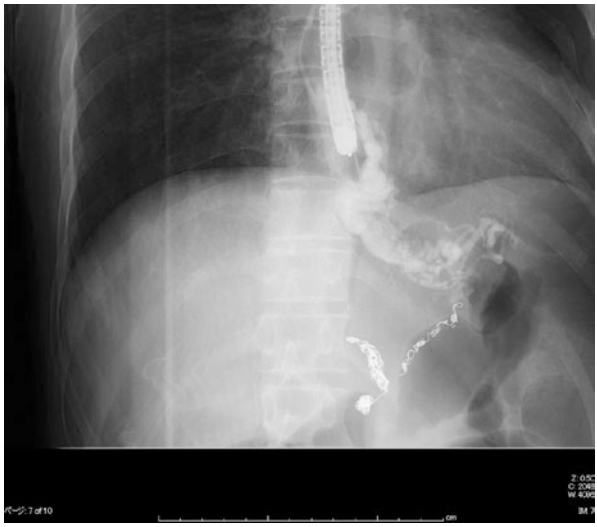


Fig. 32.4 Endoscopic varicogram showing the cardiac venous plexus clearly

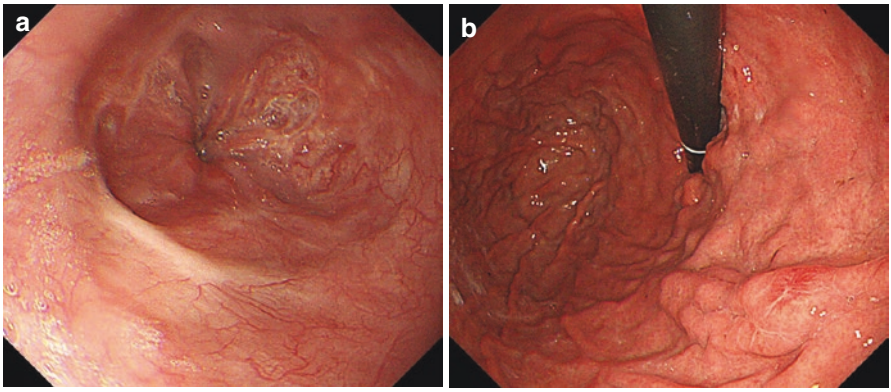


Fig. 32.5 (**a**) Endoscopic picture 1 month after EISL showing eradication of esophageal varices. (**b**) Endoscopic picture 1 month after EISL showing eradication of gastric varices

Acknowledgments I thank Dr. Niranjan Sharma PhD, Mornington Health Centre, Dunedin, New Zealand, for helpful comments.

References

1. Takase Y, Ozaki A, Orii K, Nagoshi K, Okamura T, Iwasaki Y. Injection sclerotherapy of esophageal varices for patients undergoing emergency and elective surgery. Surgery. 1982;92:474–9.
2. Takase Y, Shibuya S, Chikamori F, Orii K, Iwasaki Y. Recurrence factors studied by percutaneous transhepatic portography before and after endoscopic sclerotherapy for esophageal varices. Hepatology. 1990;11:348–52.
3. Stiegmann GV, Goff JS, Michaletz-Onody PA, Korula J, Lieberman D, Saeed ZA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med. 1992;326:1527–32.
4. Nishikawa Y, Hosokawa Y, Doi T, Shima S, Miyoshi M, Ohnishi T, et al. Simultaneous combination of endoscopic sclerotherapy and endoscopic ligation for esophageal varices. Gastrointest Endosc. 1995;42:358–60.
5. Nishikawa Y, Hosokawa Y, Doi T, Endo H, Tanimizu M, Hyodo I, et al. Evaluation of endoscopic injection sclerotherapy with and without simultaneous ligation for the treatment of esophageal varices. J Gastroenterol. 1999;34:159–62.
6. Shigemitsu T, Yoshida T, Harada T, Takeo Y, Nakamura H, Okita K. Endoscopic injection sclerotherapy with ligation versus endoscopic injection sclerotherapy alone in the management of esophageal varices: a prospective randomized trial. Hepatogastroenterology. 2000;47:733–7.
7. Umehara M, Onda M, Tajiri T, Toba M, Yoshida H, Yamashita K. Sclerotherapy plus ligation versus ligation for the treatment of esophageal varices: a prospective randomized study. Gastrointestinal Endosc. 1999;50:7–12.
8. Chikamori F, Kawashima T, Takase Y, Inoue A, Okamoto H, Kuniyoshi N, et al. Endoscopic therapy and interventional radiology for pipeline esophageal varices (in Japanese). Endosc Dig. 2010;22:1764–71.

Chapter 33
Choice of Therapy for Gastric Variceal Bleeding: Results from a Cohort Study in Japan

Naoya Murashima

Abstract There are many therapies to treat bleeding gastric varices, but comparative studies for gastric variceal bleeding have not identified which therapy is superior to all others. The Japan Society for Portal Hypertension created a registry of bleeding gastric varices for over 5 years at 31 major institutions. A variety of therapies performed in Japan during these 5 years were compared and evaluated. For emergencies, cyanoacrylate with Lipiodol injection via endoscopy was significantly more effective than conservative therapies. Balloon-occluded retrograde transvenous obliteration (B-RTO) and surgery were also effective for preventing rebleeding.

Keywords Gastric varices · Cyanoacrylate · Balloon-occluded retrograde transvenous obliteration (B-RTO) · Multicenter retrospective cohort study

33.1 Introduction

Selecting treatment for gastric variceal hemostasis should be done as soon as possible after diagnosis because of the high mortality rate associated with gastric variceal bleeding. There are many studies comparing treatments for gastric variceal bleeding, but the most reliable treatment has not yet been identified. In Japan, balloon tamponade, vasopressin infusion, and surgical procedures such as Hassab's operation [1, 2] were officially approved treatments by the Japanese health insurance system in the twentieth century. Nevertheless, clinical outcomes were not sufficient; therefore several new therapies developed around 2000 were attempted by Japanese medical institutions with approval of their respective ethical committees.

N. Murashima (✉)
Department of Gastroenterology, Mishuku Hospital, Tokyo, Japan
e-mail: murashima@mishuku.gr.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_33

This chapter addresses how to choose the safest and most reliable treatment for bleeding gastric varices from among the many treatment options available and how to decide when to repeat or change treatments, according to a cohort study conducted by the Japan Society for Portal Hypertension (JSPH) in 2009.

33.2 Methods

Endoscopic injection sclerotherapy (EIS) is a therapy where sclerosant is directly injected into a variceal cavity under endoscopy [3, 4]. Doctors in Japan can use ethanolamine oleate (EO) with iopamidol (EOI) and 1% polidocanol (Aethoxysklerol® [AS]).

Cyanoacrylate (CA) is a potent adhesive agent used for tissue adhesion. There are two CAs available in Japan. Histoacryl® is made of *N*-butyl-2-cyanoacrylate. We endoscopically inject Histoacryl into varices without dilution (Histoacryl undiluted) [5] or with Lipiodol (Histoacryl with Lipiodol) [6–14]. Alpha-cyanoacrylate monomer (Aron Alpha®) diluted with Lipiodol is also injected into gastric varices under fluoroscopy (Aron Alpha with Lipiodol) [15]. Lipiodol® is an oil-contrast media composed of iodized ethyl esters of fatty acids. Sometimes we use CA and EOI simultaneously during one endoscopic procedure (CA plus EIS).

Endoscopic variceal ligation (EVL) is a procedure in which a rubber band is directly attached to the varix through a special attachment at the tip of an endoscope [16]. Clipping is usually attempted by skillful endoscopists directly at the rupture site [17].

Balloon-occluded retrograde transvenous obliteration (B-RTO) is a radiological procedure in which sclerosant is directly infused via a balloon catheter created by Kanagawa et al. [18–21]. Conservative treatment includes balloon tamponade through the nasal cavity for direct compression of bleeding varices (balloon tamponade) and vasopressin or another vasoactive agent such as octreotide by intravenous infusion (medical treatment).

Ethanol injection [22], endoscopic snaring [23–25], transjugular intrahepatic portosystemic shunt (TIPS) [26], and liver transplantation are other treatments for gastric varices. There are a large number studies comparing many 2-treatment methods [27–33], but no studies have compared multiple methods in a large cohort.

33.3 A Large Cohort Study by the Japan Society for Portal Hypertension (JSPH)

To determine the most reliable therapy for gastric variceal bleeding, a retrospective registry study on gastric variceal bleeding treatment was conducted by the JSPH Clinical Research Committee in 2009 [34]. The gastric varices of interest were Lg-cf and Lg-f gastric varices according to recording rules by JSPH [35], not to

Sarin's classification [36]. All varices experienced bleeding within 1 month between 2004 and 2008. The end of the observation period was December 31, 2008. The episodes of bleeding treated by any other methods besides CA between 1999 and 2004 were also included. The JSPH Clinical Research Committee requested information to 110 faculties belonging to 81 main institutions and received answers from 31 institutions. The registry included all treatment methods for gastric varices, time and date, complications, and Child-Pugh classification. Rebleeding rates were calculated using Kaplan-Meier methods. Statistical differences were calculated using the log-rank test and Cox regression.

33.3.1 Initial Treatments Performed to Stop Gastric Variceal Bleeding

A total of 338 patients were registered, of whom 294 had liver cirrhosis. During the initial treatment, the most common treatment was Histoacryl with Lipiodol (83 patients, 24.6%), followed by Aron Alpha with Lipiodol (50 patients, 14.8%) and B-RTO (48 patients, 13.3%) (Fig. 33.1). As the subsequent treatment, B-RTO was the most frequently selected (70 patients, 42.7%) (Fig. 33.2).

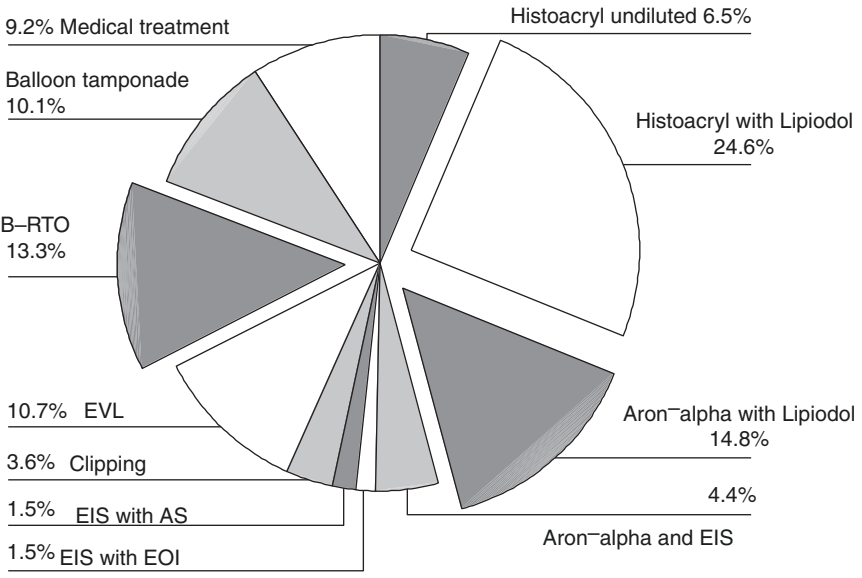


Fig. 33.1 Initial therapies performed to stop gastric variceal bleeding in Japan. *EIS* endoscopic injection sclerotherapy, *EOI* ethanolamine oleate with iopamidol, *AS* aethoxsclerol, *EVL* endoscopic variceal ligation, *B-RTO* balloon-occluded retrograde transvenous obliteration

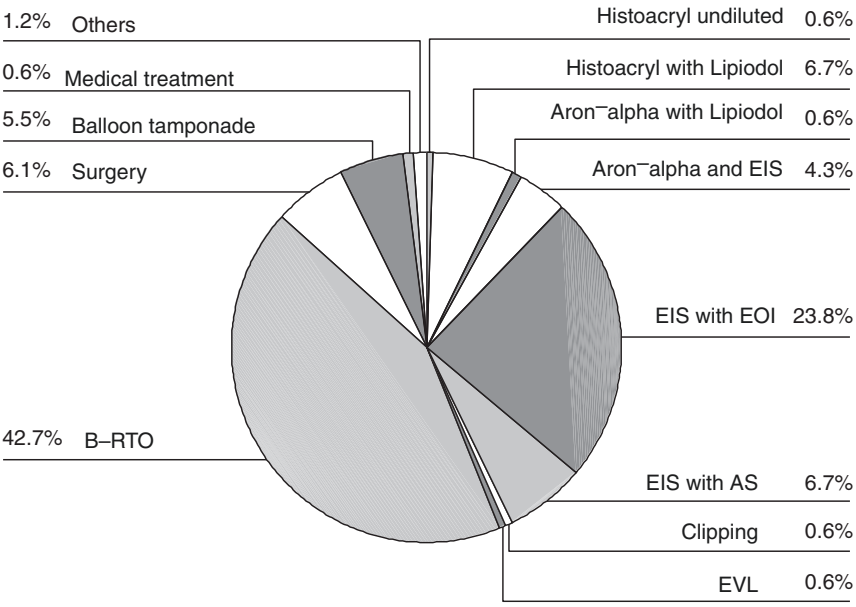


Fig. 33.2 Subsequent therapies performed after hemostasis to prevent rebleeding in Japan. *EIS* endoscopic injection sclerotherapy, *EOI* ethanolamine oleate with iopamidol, *AS* aethoxsclerol, *EVL* endoscopic variceal ligation, *B-RTO* balloon-occluded retrograde transvenous obliteration

33.3.2 Timing of Treatment

Treatment for bleeding was performed on the day of diagnosis in 63.9% of patients (mean 4.7 days). The maximum was 210 days after initial bleeding. On average, B-RTO was performed 12.84 days after bleeding, which suggests that B-RTO should be performed as an elective procedure (Table 33.1).

33.3.3 Complications

Table 33.2 shows complications in each therapy during/after the initial treatment. With undiluted Histoacryl, bleeding at the puncture site occurred in 6.3% of patients. Aron Alpha with Lipiodol was also associated with similar complications (8.0%). Histoacryl with Lipiodol did not provoke pulmonary infarction, the most serious complication previously described [37–39].

Table 33.1 Interval (days) between first bleeding and initial treatment

Treatment method	Mean (day)	S.D.	Median (day)	Max (day)
Histoacryl undiluted	0.95	0.42	0	8
Histoacryl with Lipiodol	3.43	1.07	0	69
Aron Alpha with Lipiodol	6.70	4.46	0	219
Aron Alpha and EIS	7.87	4.23	0	59
EIS with EOI	3.40	3.40	0	17
EIS with AS	0.20	0.20	0	1
Clipping	0.42	0.19	0	2
EVL	3.22	2.68	0	96
B-RTO	12.84	4.03	1	147
Balloon tamponade	0.18	0.07	0	1
Medical therapy	3.45	1.79	0	44

EIS endoscopic injection sclerotherapy, *EOI* ethanolamine oleate with iopamidol, *AS* aethoxysclerol, *EVL* endoscopic variceal ligation, *B-RTO* balloon-occluded retrograde transvenous obliteration

Table 33.2 Complications in each therapy during/after the initial treatment

Treatment method	Complication (number of patients)
Histoacryl undiluted	Bleeding from injection site (1)
Aron Alpha only	None
Histoacryl with Lipiodol	Ascites (1), gastric ulcer bleeding (1), liver damage (1)
Aron Alpha with Lipiodol	Bleeding from injection site (4), liver failure (1)
Aron Alpha and EIS	Ascites (1), fever (1), bleeding from injection site (1), ARDS (1), liver failure (1)
EIS with EOI	Ascites (1)
EIS with AS	Hypovolemic shock (1)
Clipping	Hypovolemic shock (1)
EVL	Pneumonia (1), esophageal variceal rupture (1)
B-RTO	Peumonia (1), ascites (2), fever (1)
Balloon tamponade	Liver failure (1)
Medical treatment	Liver failure (1)

EIS endoscopic injection sclerotherapy, *EOI* ethanolamine oleate with iopamidol, *AS* aethoxysclerol, *EVL* endoscopic variceal ligation, *B-RTO* balloon-occluded retrograde transvenous obliteration, *ARDS* acute respiratory distress syndrome

33.3.4 Rebleeding Rates by Initial Treatment Method

Histoacryl undiluted was used in 22 patients. Rebleeding occurred in one patient on day 4. The rebleeding rates were 5.0% at 30 days and 24.0% at 100 days. Histoacryl with Lipiodol was used in 83 patients, of whom one rebled on day 1. The rebleeding rates were 4.2% at 30 days and 10.1% at 100 days. Aron Alpha with Lipiodol was used in 50 patients. The rebleeding rates were 5.3% at 30 days and 16.1% at

100 days. CA plus EIS was used in 15 patients. The rebleeding rates were 13.8% at 7 days, 26.1% at 30 days, and 26.1% at 100 days. EIS with EOI was used in five patients, and there were no rebleeding events within 100 days. EIS with AS was used in five patients. One patient rebled at 21 days. The rebleeding rate was 50% at 30 days. The maximum observation period was 22 days. Clipping was performed in 12 patients. The rebleeding rates were 20.0% at 7 days, 33.3% at 30 days, and 50.0% at 100 days. EVL was performed in 36 patients. It was not possible to stop bleeding in two patients. The rebleeding rates were 9.9% at 7 days and 17.2% at 30 days. B-RTO was performed in 45 patients. None of them rebled within 30 days. The rebleeding rate was 5.6% at 100 days. Balloon tamponade was used in 34 patients. One patient rebled on day 1. The rebleeding rate was 19.5% at 7 days. Medical treatment was used in 31 patients. There was no bleeding within 7 days. The rebleeding rates were 6.7% at 30 days and 30.0% at 100 days.

Figure 33.3 shows rebleeding rates in injection of CA with Lipiodol (Histoacryl with Lipiodol plus Aron Alpha with Lipiodol) compared with those in medical treatment or balloon tamponade. One hundred and thirty-three patients treated with CA with Lipiodol were compared to 65 patients who underwent conservative treatment (balloon tamponade and medical treatment). One patient who received CA with Lipiodol rebled on day 1 and another rebled on day 8. The rebleeding rate was 4.3%

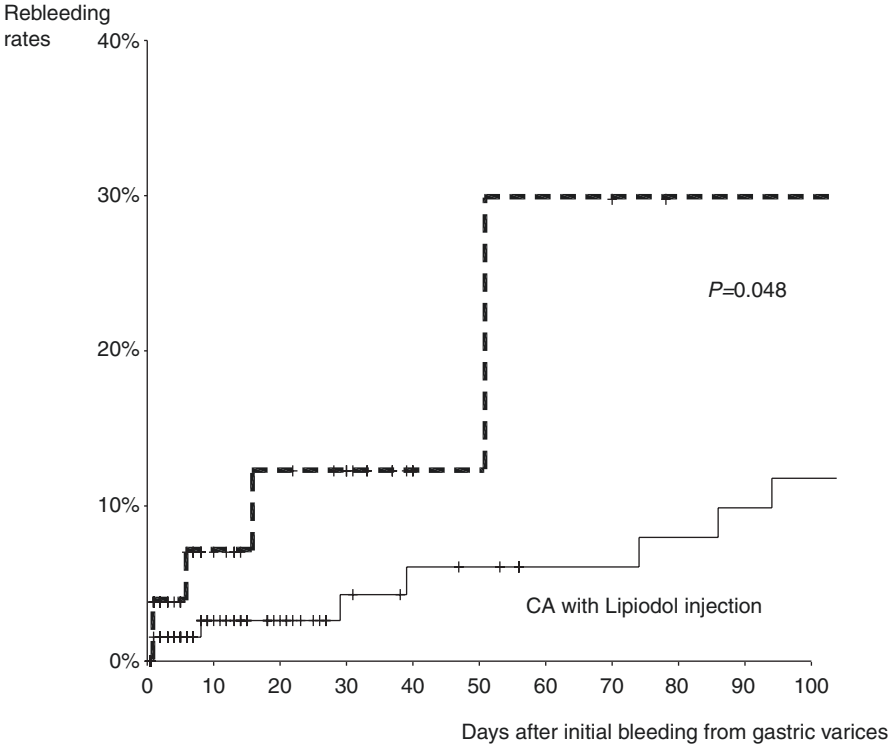


Fig. 33.3 Rebleeding rates for cyanoacrylate (CA) with Lipiodol injection (CA with Lipiodol) compared with medical treatment or balloon tamponade. *CA* cyanoacrylate

at 30 days. With conservative treatment, the rebleeding rates were 7.0% at 7 days and 12.2% at 30 days. The difference between the rebleeding rate in patients treated with CA with Lipiodol and that in patients treated with conservative treatment at 30 days was significant ($P = 0.048$).

Rebleeding rates with B-RTO were significantly lower ($P = 0.010$) than those with conservative treatment (Fig. 33.4).

33.3.5 Factors Affecting Rebleeding Rates in Patients with Cirrhosis

The rebleeding rates in each treatment method were compared with those in medical treatment or balloon tamponade using univariate analysis. B-RTO and CA with Lipiodol were associated with significantly less rebleeding. The hazard ratio (HR) was 0.106 and 95% confidence intervals (95% CI) was 0.017–0.659 for B-RTO and HR was 0.214 and 95% CI was 0.056–0.812 for CA with Lipiodol, respectively. However, there was no significant difference between medical treatment or balloon tamponade and other treatments such as clipping or EVL.

Gastric variceal rebleeding rates were significantly higher ($P = 0.024$) in patients with Child C cirrhosis than in those with Child A or B cirrhosis (Fig. 33.5).

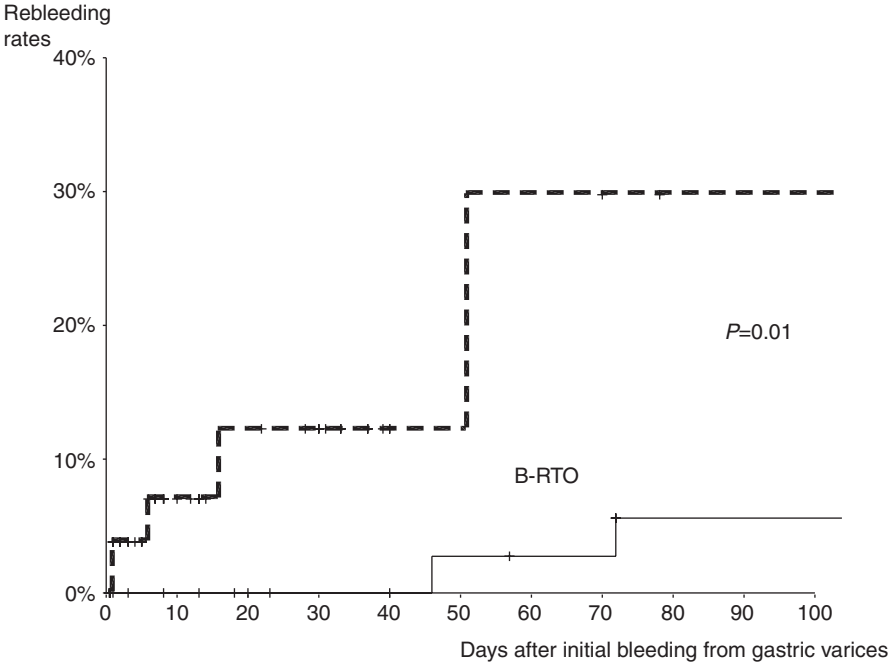


Fig. 33.4 Rebleeding rates after B-RTO versus medical treatment or balloon tamponade. *B-RTO* balloon-occluded retrograde transvenous obliteration

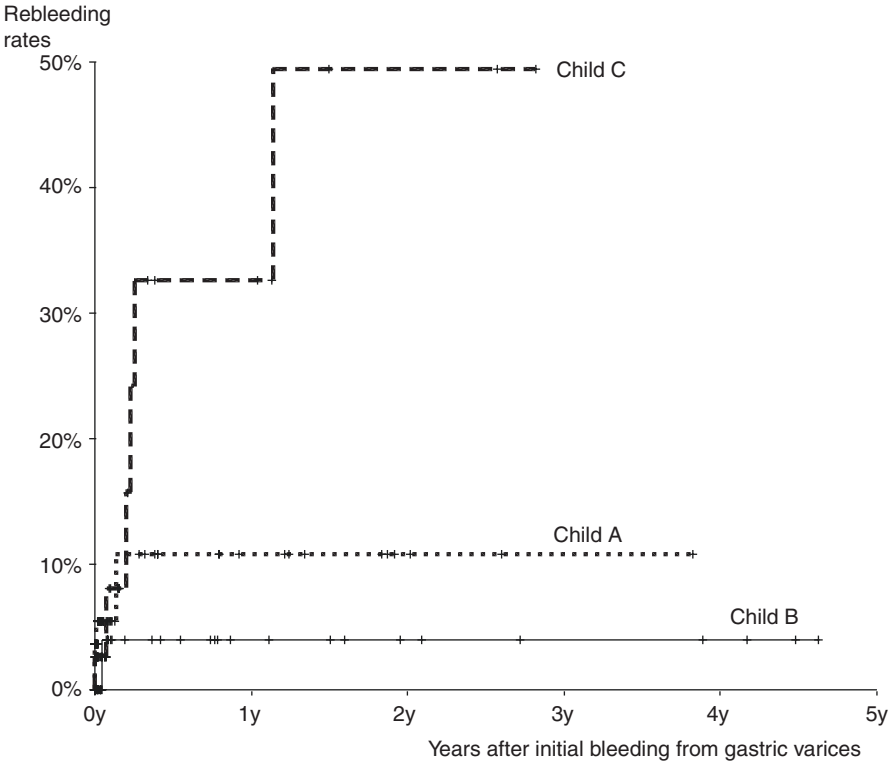


Fig. 33.5 Rebleeding rates according to Child classification in patients with cirrhosis

Table 33.3 Rebleeding rates in each therapy compared with medical or balloon tamponade therapy, adjusted by gender, age, and Child classification in patients with cirrhosis (multivariate analysis)

Treatment method	No. of cases	Hazard ratio	95% CI		*P*
			Lower	Upper	
Medical Rx or Balloon tamponade	60	1	–	–	–
Histoacryl undiluted	16	0.899	0.163	4.361	0.903
CA with Lipiodol	117	0.263	0.078	0.885	0.031
Clipping	12	2.115	0.565	7.961	0.266
EVL	31	0.952	0.243	3.735	0.944
B-RTO	39	0.409	0.104	1.607	0.200

Rx treatment, *CA* cyanoacrylate, *EVL* endoscopic variceal ligation, *B-RTO* balloon-occluded retrograde transvenous obliteration

Table 33.3 shows the multivariate Cox proportional hazards analysis comparing various treatments with medical treatment or balloon tamponade as the referent group adjusted for gender, age, and Child classification. Only CA with Lipiodol was found to be a significant inhibitor of rebleeding (HR 0.263; 95% CI 0.078–0.885).

33.3.6 Rebleeding Rates After Both Initial and Subsequent Treatments

Initial treatment to stop bleeding and prevention of rebleeding can be thought as one therapeutic process. Table 33.4 shows rebleeding rates from gastric varices and from the gastrointestinal tract at 100 days calculated using the Kaplan-Meyer method according to the initial and subsequent treatments. The most frequently performed treatment was Histoacryl with Lipiodol without subsequent treatment ($n = 49$). Rebleeding from varices occurred in six patients (12.2%), and gastrointestinal bleeding after 100 days occurred in 14.4% of patients. Aron Alpha with Lipiodol monotherapy was used in 29 patients. Rebleeding occurred in three (10.3%) patients. B-RTO alone was used in 39 patients. Rebleeding occurred in five (12.8%) patients. These types of monotherapies were associated with a rebleeding rate of approximately 10%.

Table 33.4 Rebleeding rates from gastric varices and gastrointestinal tract according to initial and subsequent treatment

Initial treatment	Subsequent treatment	No. of patients	No. of rebleeding cases from gastric varices (%)	Rebleeding rates (%) from gastrointestinal tract at 100 days after initial bleeding (Kaplan-Meyer method)
Histoacryl undiluted	None	8	2 (16.7)	30.0
Histoacryl undiluted	B-RTO	6	0	0
Histoacryl with Lipiodol	None	49	6 (12.2)	14.4
Histoacryl with Lipiodol	B-RTO	10	0	11.1
Histoacryl with Lipiodol	EIS by EOI	18	1 (5.6)	5.8
Aron Alpha with Lipiodol	None	29	3 (10.3)	16.1
Aron Alpha wuth Lipiodol	B-RTO	10	2 (20.0)	0
Aron Alpha and EIS	None	11	3 (27.3)	35.3
Clipping	None	6	5 (83.3)	67.7
EVL	None	13	4 (30.8)	43.9
EVL	B-RTO	6	1 (16.7)	20.0
B-RTO	None	39	5 (12.8)	0
Balloon tamponade	None	8	3 (37.5)	50.0
Balloon tamponade	B-RTO	6	1 (16.7)	0
Balloon tamponade	Surgery	5	0	0
Medical treatment	B-RTO	22	1 (4.5)	4.5

EIS endoscopic injection sclerotherapy, *EOI* ethanolamine oleate with iopamidol, *AS* aethoxsclerol, *EVL* endoscopic variceal ligation, *B-RTO* balloon-occluded retrograde transvenous obliteration

Subsequent treatment made it possible to lower rebleeding rates. Histoacryl undiluted followed by B-RTO was used in six patients, where no rebleeding was observed. Histoacryl with Lipiodol followed by B-RTO was used in ten patients, where no rebleeding was observed. No bleeding was observed in five patients treated with balloon tamponade followed by surgery.
Rebleeding rates from any gastrointestinal tract location at 100 days were calculated using the Kaplan-Meier method for each treatment method. The rebleeding rate for Histoacryl with Lipiodol followed by B-RTO was 11.1% and Histoacryl with Lipiodol followed by EIS was 5.8%. Aron Alpha with Lipiodol followed by B-RTO was 0% and medical treatment followed by B-RTO was 4.5%.

33.3.7 Factors Affecting Survival Rates

Factors affecting survival in patients with cirrhosis ($n = 294$) were calculated using Cox's proportional hazard model (multivariate analysis). Child C (HR 3.04; 95% CI 2.12–4.36), hepatocellular carcinoma (HR 3.08; 95% CI 1.96–4.79), and the presence of rebleeding (HR 2.21; 95%CI 1.29–3.50) were significant and independent factors affecting survival in patients with cirrhosis ($P < 0.01$).

33.4 Conclusions

This long-term cohort study in Japan revealed that prevention of rebleeding is one of the significant factors associated with improved survival in patients with cirrhosis. As an initial treatment, CA with Lipiodol is a safer and more effective treatment than conservative treatment. If the bleeding is not serious and the patient has preserved liver function, B-RTO is an alternative option. When the initial treatment achieves hemostasis, subsequent treatment for prevention of rebleeding is necessary. B-RTO and open surgery are strongly recommended in patients with preserved liver function. In patients with Child C cirrhosis, repeat CA with Lipiodol by a well-trained endoscopist should be considered in Japan. Medical treatment can still be considered, although it is not as effective. TIPS [40] and liver transplantation are the final choices to cure patients in Japan. The consensus in Europe is discussed in other manuscripts [41, 42].

References

1. Hassab MA. Gastro-esophageal decongestion and splenectomy GEDS (Hassab), in the management of bleeding varices; review of literature. Int Surg. 1998;83:38–41.
2. Tomikawa M, Hashizume M, Saku M, Tanoue K, Ohta M, Sugimachi K. Effectiveness of gastric devascularization and splenectomy for patients with gastric varices. J Am Coll Surg. 2000;191:498–503.

3. Sarin SK, Sachdev G, Nanda R, Misra SP, Broor SL. Endoscopic sclerotherapy in the treatment of gastric varices. Br J Surg. 1988;75:747–50.
4. Gimson AE, Westaby D, Williams R. Endoscopic sclerotherapy in the management of gastric variceal haemorrhage. J Hepatol. 1991;13:274–8.
5. Soehendra N, Grimm H, Nam VC, Berger B. N-butyl-2-cyanoacrylate: a supplement to endoscopic sclerotherapy. Endoscopy. 1987;19:221–4.
6. Stoesslein F, Ditscherlein G, Romaniuk PA. Experimental studies on new liquid embolization mixtures (histoacryl-lipiodol, histoacryl-panthopaque). Cardiovasc Intervent Radiol. 1982;5:264–7.
7. Seewald S, Ang TL, Imazu H, Naga M, Omar S, Groth S, et al. A standardized injection technique and regimen ensures success and safety of N-butyl-2-cyanoacrylate injection for the treatment of gastric fundal varices. Gastrointest Endosc. 2008;68:447–54.
8. Ogawa K, Ishikawa S, Naritaka Y, Shimakawa T, Wagatsuma Y, Katsube A, et al. Clinical evaluation of endoscopic injection sclerotherapy using n-butyl-2-cyanoacrylate for gastric variceal bleeding. J Gastroenterol Hepatol. 1999;14:245–50.
9. Ramond MJ, Valla D, Mosnier JF, Degott C, Bernuau J, Rueff B, et al. Successful endoscopic obturation of gastric varices with butyl cyanoacrylate. Hepatology. 1989;10:488–93.
10. Feretis C, Tabakopoulos D, Benakis P, Xenofontos M, Golematis B. Endoscopic hemostasis of esophageal and gastric variceal bleeding with Histoacryl. Endoscopy. 1990;22:282–4.
11. D'Imperio N, Piemontese A, Baroncini D, Billi P, Borioni D, Dal Monte PP, et al. Evaluation of undiluted N -butyl-2 -cyanoacrylate in the endoscopic treatment of upper gastrointestinal tract varices. Endoscopy. 1996;28:239–43.
12. Marques P, Maluf-Filho F, Kumar A, Matuguma SE, Sakai P, Ishioka S. Long-term outcomes of acute gastric variceal bleeding in 48 patients following treatment with cyanoacrylate. Dig Dis Sci. 2008;53:544–50.
13. Huang YH, Yeh HZ, Chen GH, Chang CS, Wu CY, Poon SK, et al. Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacryl) injection: long-term efficacy and safety. Gastrointest Endosc. 2000;52:160–7.
14. Akahoshi T, Hashizume M, Shimabukuro R, Tanoue K, Tomikawa M, Okita K, et al. Long-term results of endoscopic Histoacryl injection sclerotherapy for gastric variceal bleeding: a 10-year experience. Surgery. 2002;131:S176–81.
15. Obara K, Ohira H, Sakamoto H, Iwasaki K, Morito T, Kasukawa R. Endoscopic injection sclerotherapy with alpha-cyanoacrylate monomer for emergent bleeding from isolated gastric varices—report of 3 cases. Gastroenterol Endsc. 1989;32:3209–16. (In Japanese).
16. Shiha G, El-Sayed SS. Gastric variceal ligation: a new technique. Gastrointest Endosc. 1999;49:437–41.
17. Koutsomanis D. Endoscopic clipping for bleeding varices. Gastrointest Endosc. 1994;40:126–7.
18. Kanagawa H, Mima S, Kouyama H, Gotoh K, Uchida T, Okuda K. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. J Gastroenterol Hepatol. 1996;11:51–8.
19. Hiraga N, Aikata H, Takaki S, Kodama H, Shirakawa H, Imamura M. The long-term outcome of patients with bleeding gastric varices after balloon-occluded retrograde transvenous obliteration. J Gastroenterol. 2007;42:663–72.
20. Shiba M, Higuchi K, Nakamura K, Itani A, Kuga T, Okazaki H, et al. Efficacy and safety of balloon-occluded endoscopic injection sclerotherapy as a prophylactic treatment for high-risk gastric fundal varices: a prospective, randomized, comparative clinical trial. Gastrointest Endosc. 2002;56:522–8.
21. Matsumoto A, Hamamoto N, Nomura T, Hongou Y, Arisaka Y, Morikawa H, et al. Balloon-occluded retrograde transvenous obliteration of high risk gastric fundal varices. Am J Gastroenterol. 1999;94:643–9.
22. Sarin SK, Jain AK, Jain M, Gupta R. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. Am J Gastroenterol. 2002;97:1010–5.
23. Yoshida T, Hayashi N, Suzumi N, Miyazaki S, Terai S, Itoh T, et al. Endoscopic ligation of gastric varices using a detachable snare. Endoscopy. 1994;26:502–5.

24. Harada T, Yoshida T, Shigemitsu T, Takeo Y, Tada M, Okita K. Therapeutic results of endoscopic variceal ligation for acute bleeding of oesophageal and gastric varices. J Gastroenterol Hepatol. 1997;12:331–5.
25. Yoshida T, Harada T, Shigemitsu T, Takeo Y, Miyazaki S, Okita K. Endoscopic management of gastric varices using a detachable snare and simultaneous endoscopic sclerotherapy and O-ring ligation. J Gastroenterol Hepatol. 1999;14:730–5.
26. Barange K, Péron JM, Imani K, Otal P, Payen JL, Rousseau H, et al. Transjugular intrahepatic portosystemic shunt in the treatment of refractory bleeding from ruptured gastric varices. Hepatology. 1999;30:1139–43.
27. Oho K, Iwao T, Sumino M, Toyonaga A, Tanikawa K. Ethanolamine oleate versus butyl cyanoacrylate for bleeding gastric varices: a nonrandomized study. Endoscopy. 1995;27:349–54.
28. Tantau M, Crisan D, Popa D, Vesa S, Tantau A. Band ligation vs. N-butyl-2-cyanoacrylate injection in acute gastric variceal bleeding: a prospective follow-up study. Ann Hepatol. 2014;13:75–83.
29. Mahadeva S, Bellamy MC, Kessel D, Davies MH, Milson XE. Cost-effectiveness of N-butyl-2-cyanoacrylate (histoacryl) glue injections versus transjugular intrahepatic portosystemic shunt in the management of acute gastric variceal bleeding. Am J Gastroenterol. 2003;98:2688–93.
30. Lo GH, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. Hepatology. 2001;33:1060–4.
31. Maluf-Filho F, Sakai P, Ishioka S, Matsuguma SE. Sclerosis versus cyanoacrylate endoscopic injection for the first episode of variceal bleeding: a prospective, controlled, randomized study and in Child-Pugh class C patients. Endoscopy. 2001;33:421–7.
32. Lo GH, Liang HL, Chen WC, Chen MH, Lai KH, Hsu PI, et al. A prospective, randomized controlled trial of transjugular intrahepatic portosystemic shunt versus cyanoacrylate injection in the prevention of gastric variceal rebleeding. Endoscopy. 2007;39:679–85.
33. Hong CH, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, et al. Treatment of patients with gastric variceal hemorrhage: endoscopic N-butyl-2 cyanoacrylate injection versus balloon-occluded retrograde transvenous obliteralition. J Gastroenterol Hepatol. 2009;24:372–8.
34. Murashima N, Watanabe N, Ohta M, Obara K, Oho K, Kokubu S, et al. Evaluation of the therapies for bleeding gastric varices in Japan; a retrospective multi-center cohort study. Jpn J Portal Hypertens. 2010;16:88–103. (in Japanese).
35. Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc. 2010;22:1–9.
36. Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. Hepatology. 1992;16:1343–9.
37. Fry LC, Neumann H, Olano C. Efficacy, complications and clinical outcomes of endoscopic sclerotherapy with N-butyl-2-cyanoacrylate for bleeding gastric varices. Dig Dis. 2008;26:300–3.
38. Alexander S, Korman MG, Sievert W. Cyanoacrylate in the treatment of gastric varices complicated by multiple pulmonary emboli. Intern Med J. 2006;36:462–5.
39. Singer AD, Fananapazir G, Maufa F, Narra S, Ascher S. Pulmonary embolism following 2-octyl-cyanoacrylate/lipiodol injection for obliteration of gastric varices: an imaging perspective. J Radiol Case Rep. 2012;6:17–22.
40. García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 2010;362:2370–9.
41. de Franchis R, Faculty Baveno V. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2010;53:762–8.
42. Weil D, Cervoni JP, Fares N, Rudler M, Bureau C, Plessier A, et al. Management of gastric varices: a French national survey. Eur J Gastroenterol Hepatol. 2016;28:576–81.

Chapter 34
Endoscopic Treatment of Gastric Varices: Histoacryl Method

Hiroaki Iwase

Abstract The endoscopic injection of cyanoacrylate glue (Histoacryl) has been successfully used to obliterate gastric varices in various parts of the world. To perform this treatment safely and effectively, the Histoacryl should be diluted with 5% Lipiodol (1:1) to lengthen the cyanoacrylate polymer and allow fluoroscopic monitoring. A mixture of Histoacryl and 5% Lipiodol should be injected to fill the gastric varices and the juxta-variceal portions of their inflow/outflow veins. Most gastric varices consist of a single varicose vessel and can be successfully obstructed with two injections. In the case of large gastric varices consisting of multiple varices, Histoacryl should be injected not only into the main varices but also into any small varices and connecting ramifications. The fluoroscopic monitoring of the injection procedure is very important for reducing the risk of complications and ensuring that gastric varices are completely obliterated. Assessments of variceal anatomy might provide useful clinical information that will lead to improvements in the treatment strategies for such patients. The endoscopic injection of cyanoacrylate glue (Histoacryl) under fluoroscopic guidance can rapidly halt life-threatening gastric variceal bleeding and remove patients' long-term fears regarding the risk of rebleeding.

Keywords Gastric variceal bleeding · Histoacryl · Vascular anatomy · Lipiodol Fluoroscopic observation

H. Iwase
Department of Gastroenterology, National Hospital Organization, Nagoya Medical Centre, Nagoya, Aichi, Japan
e-mail: iwaseh@nnh.hosp.go.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_34

34.1 Introduction

Gastric varices (GV) are often seen in patients with portal hypertension. Although GV are associated with a lower risk of bleeding than esophageal varices (EV), bleeding GV are severe and potentially life-threatening complications [1]. Endoscopic injection sclerotherapy using conventional sclerosants and endoscopic variceal ligation have been widely accepted as treatments for bleeding EV, both for the management of active bleeding and the prevention of recurrent bleeding over the long term [2, 3]. However, in the case of bleeding GV, such endoscopic therapies yield poor control of bleeding and are associated with a high frequency of severe complications [4, 5].

In contrast to standard sclerosants, the tissue adhesive butyl cyanoacrylate (cyanoacrylate glue) polymerizes immediately and induces vascular obliteration on contact with blood. The endoscopic intravascular injection of cyanoacrylate glue was originally proposed by Soehendra et al. in 1986 as a therapeutic option for large bleeding esophagogastric varices [6]. Subsequent studies have suggested that this method might be useful for achieving GV obliteration, and it has been successfully employed for the treatment of GV bleeding worldwide [7, 8]. However, there are still some controversies concerning the optimal technique, and little information is available about the long-term effects of such treatment and the most appropriate management strategies for special types of GV in the gastric cardia and gastric body.

We have conducted endoscopic obliteration with cyanoacrylate glue (Histoacryl®; Braun Melsungen, Germany) for GV bleeding since 1992 [9] based on evaluations of gastric vascular anatomy [10] and have used this technique to save the lives of patients with GV bleeding [9, 11]. To perform this treatment safely and effectively, Histoacryl diluted with 5% Lipiodol (1:1) should be carefully injected into the GV under fluoroscopic guidance while taking the vascular anatomy of the GV into account. This paper mainly describes the technique we employ for the treatment of GV.

34.2 Gastric Vascular Anatomy

According to evaluations of GV anatomy performed with color Doppler endoscopic ultrasonography (CDEUS), varicography, and three-dimensional computed tomography (3D-CT), we consider that the anatomy of GV can be broadly divided into two types: type 1 (Fig. 34.1a), in which the vascular anatomy of the GV consists of a single varicose vessel of almost the same diameter as the inflow/outflow vein without any noticeable ramifications, and type 2 (Fig. 34.1b), in which the vascular anatomy of the GV consists of multiple varicose vessels with complex connecting ramifications [9–11]. Associations have been detected among the endoscopic features, locations, and vascular anatomy of GV. Type 1 is the most common type of GV, although it is found almost exclusively in cases of so-called isolated GV (86%), whereas type 2 is generally encountered in special cases of GV in which EV extend

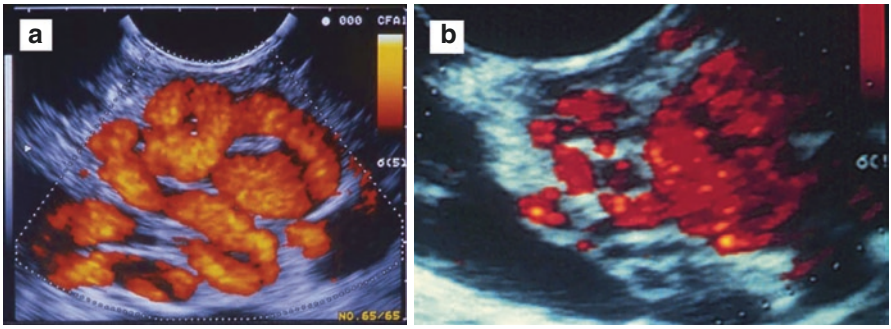


Fig. 34.1 (**a**) CDEUS image of a type 1 GV shows only one inflow/outflow vein and one varicose vessel without ramifications. (**b**) CDEUS image of a type 2 GV shows multiple varicose vessels connected to one another with complex ramifications

into the gastric cardia and body (91%) [10]. The endoscopic injection of Histoacryl should be carried out in a manner that takes the vascular anatomy of the GV into consideration.

34.3 Treatment Procedure

The procedure is visualized using a forward-view videoendoscope (Olympus Optical Co., Ltd., Tokyo, Japan), and a 23-gauge needle (Top Co., Ltd., Japan) is used for the injections. Most procedures require a retroflexed view for visualization and puncture. Before the intravascular puncture procedure, 1 mL of Histoacryl is drawn up into an ordinary 2.5-mL plastic syringe and diluted with 5% Lipiodol (1:1) (producing the Histoacryl mixture) to lengthen the cyanoacrylate polymer and allow fluoroscopic monitoring. The 23-gauge needle should be rinsed with distilled water or 50% glucose before and after the injection.

In patients with bleeding GV, an attempt should be made to puncture the GV as near to the bleeding site as possible. If it is impossible to precisely puncture the target varices because of massive bleeding, or if no Histoacryl has been prepared, e.g., in cases involving emergent endoscopy, the short-term use of a balloon or endoscopic clips to achieve temporary hemostasis is recommended. Once the bleeding has completely stopped, i.e., after approximately 6 h, the Histoacryl should be injected into the GV at the bleeding site, which will be readily recognizable as it will be covered with clotted blood and fibrin. The exact position of the needle relative to the planned GV puncture site should be checked before the injection procedure. The intravascular puncturing of large varices is easy. However, paravascular puncturing causes mucosal swelling. When Histoacryl is injected into the gastric muscular layer, blood might spurt from the puncture site after the needle is pulled out. Deep puncturing should be avoided.Therefore, superficial puncturing is recommended for small GV. The flow of the Histoacryl mixture can be monitored

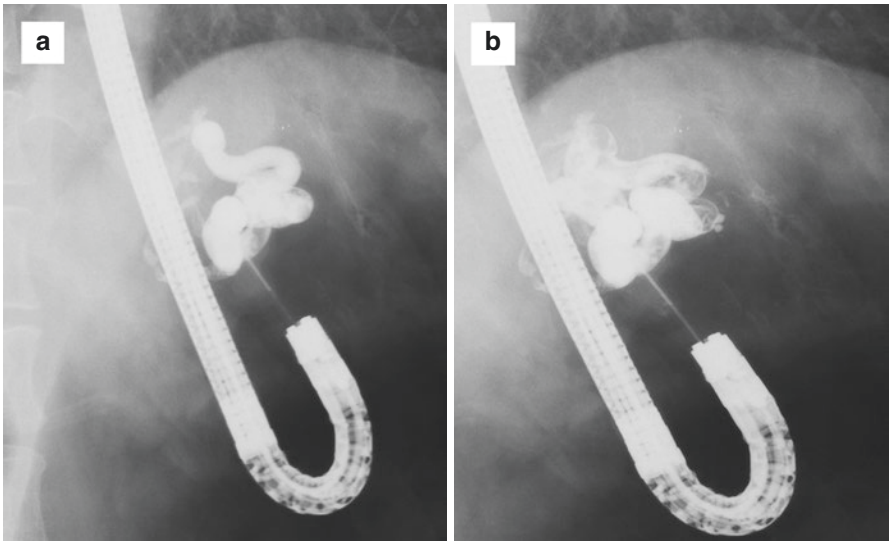


Fig. 34.2 X-ray varicography images obtained in a representative patient during the endoscopic injection of a mixture of Histoacryl and Lipiodol. The GV, which consisted of a single varicose vessel, was completely obstructed via two injections of a mixture of Histoacryl and Lipiodol. (**a**) X-ray images obtained during the second injection. The injection was halted when the mixture of Histoacryl and Lipiodol filled the region extending from the puncture site to the juxta-variceal portion of the outflow vein. (**b**) X-ray images obtained during the first injection. The injection was halted when the mixture of Histoacryl and Lipiodol filled the region extending from the puncture site to the juxta-variceal portion of the inflow vein

fluoroscopically during the injection, and the injection should be continued until the Histoacryl mixture has filled the GV and the juxta-variceal portions of their inflow/outflow veins.

The first injection should be halted when the Histoacryl mixture starts to move from the puncture site to the juxta-variceal portion of the outflow veins (Fig 34.2a), after which a second injection is performed at the same or a different site to occlude the inflow veins (Fig 34.2b). Most GV consist of a single varicose vessel and can be completely obstructed via two injections of the Histoacryl mixture. In fact, some small GV can be obstructed with a single injection. The adequacy of the GV obliteration can be judged based on the shape of the Histoacryl mixture cast. In the case of large type 2 GV, the Histoacryl mixture should be injected into both the main and small varices and any complex connecting ramifications.

34.4 Case Reports

Case 1 This case involved a 54-year-old female patient with decompensated alcoholic liver cirrhosis. At the previous hospital, she underwent endoscopy for anemia, and the endoscopist found blood spurting from a small fundal varix (Fig. 34.3a) and

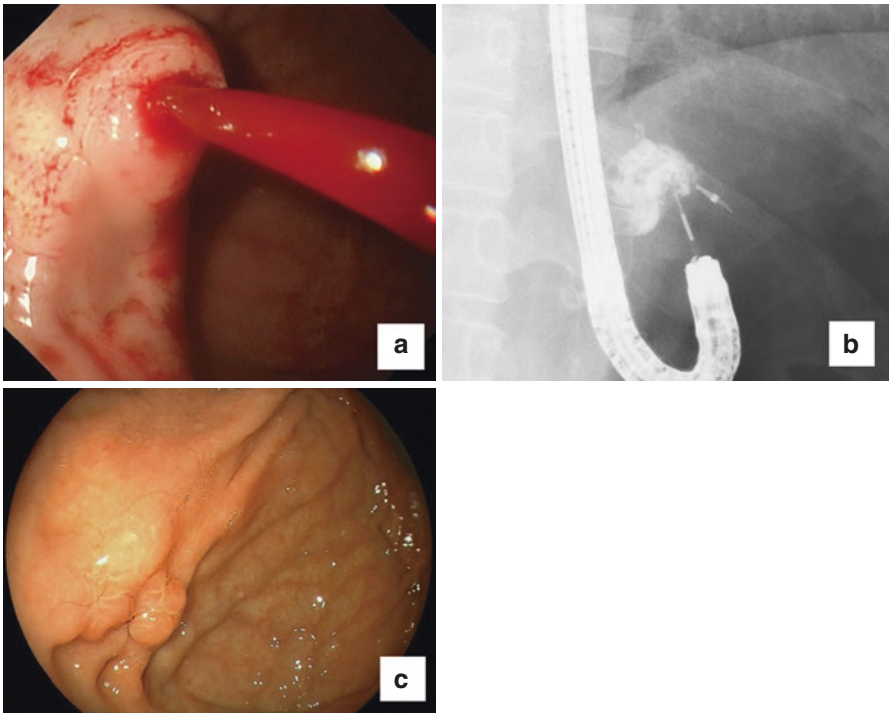


Fig. 34.3 (**a**) Endoscopic appearance of blood spurting from a small fundal varix. (**b**) X-ray varicography showing that the varicose vein has been completely occluded after two endoscopic injections of a mixture of Histoacryl and Lipiodol. (**c**) Endoscopic image obtained at 6 postoperative months showing a completely eradicated GV

immediately subjected the bleeding site to endoscopic clipping. The bleeding was temporarily arrested. The patient received a 4-unit blood transfusion and was referred to our hospital. At our hospital, two endoscopic intravascular injections of 1.5 mL and 1.0 mL, respectively, of the Histoacryl mixture were administered near the clipping site (Fig. 34.3b). The GV was completely eradicated after 6 months (Fig. 34.3c), and since then there has been no further variceal bleeding.

Case 2 A 72-year-old female patient with liver cirrhosis of unknown cause was admitted after producing bloody stools. She had previously undergone endoscopic obliteration with Histoacryl for large GV. Emergent endoscopy revealed blood oozing from the GV, which had been almost completely obliterated. Endoscopic clipping was not effective to stop the bleeding (Fig. 34.4a); therefore it was arrested with a Sengstaken-Blakemore tube. After 6 h, i.e., after the bleeding stopped, 1 mL of the Histoacryl mixture was injected endoscopically into the rupture site, which was covered with a blood clot, under fluoroscopic observation. The remaining small varicose vessels and the associated ramification were fully obstructed with the Histoacryl mixture (Fig. 34.4b), and the bleeding stopped immediately (Fig. 34.4c). No recurrent bleeding has occurred since.

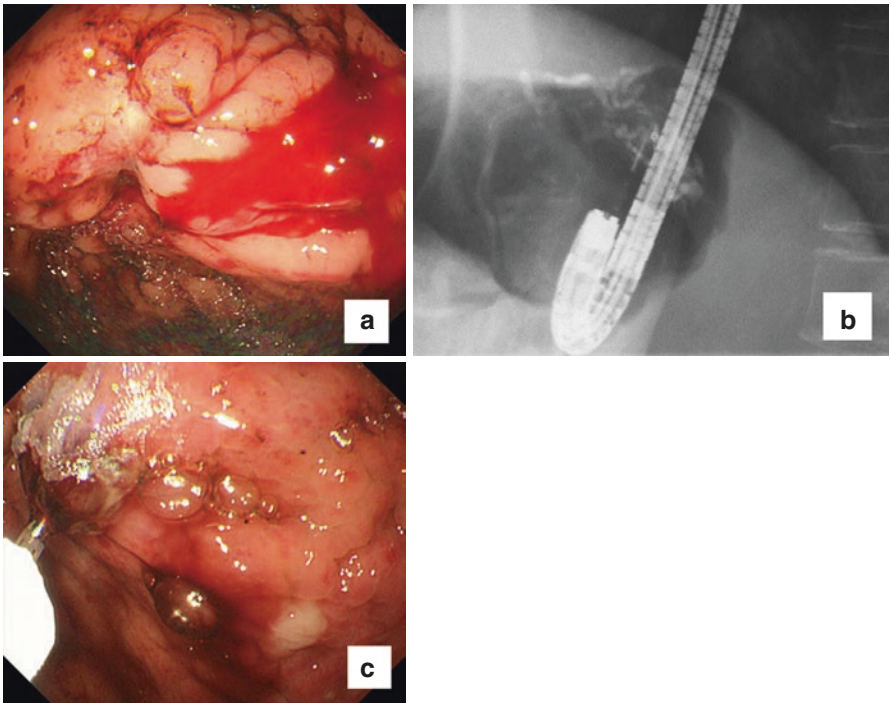


Fig. 34.4 (**a**) Image obtained during emergent endoscopy showing blood oozing from the remaining small varices. The bleeding was arrested with a Sengstaken-Blakemore tube. (**b**) Varicography showing that the small varicose veins and the remaining ramification has been completely filled with a mixture of Histoacryl and Lipiodol. (**c**) Endoscopic image showing that the bleeding has arrested just after the injection of the mixture of Histoacryl and Lipiodol

34.5 Discussion

Regarding our long-term results of endoscopic obliteration with Histoacryl, the primary hemostasis success rate was 95.8% among 71 patients with GV bleeding [11]. This primary hemostasis rate was comparable to or better than those of 90–96% described in other reports [8, 12]. Nine patients (two patients with type 1 GV and seven patients with type 2 GV) developed recurrent GV bleeding over the 17-year study period [11]. Most cases of recurrent GV bleeding were due to incomplete obliteration and occurred within 1 year of the primary hemostasis. The so-called isolated GV, i.e., those with type 1 vascular anatomy (the most common type of GV), were easily obstructed via one or two injections of Histoacryl, indicating that the condition is associated with a very low long-term risk of recurrent bleeding. In the patients with type 2 GV, such as the patient in Case 2, the residual small varicose vessels left after the endoscopic obliteration were found to be associated with a risk of recurrent bleeding. In general, the recurrent bleeding was not severe and could be controlled via repeated endoscopic injections of Histoacryl. However, in a few

patients who had very complex vascular anatomies and had developed collateral vein systems, complete obliteration of the GV could not be achieved [11]. In the patients who respond poorly to re-injection with Histoacryl, non-endoscopic techniques, such as surgical procedures or transjugular intrahepatic portosystemic shunts, are effective alternatives. During a long survey performed at our institution, the main causes of death among patients who underwent endoscopic obliteration for GV were shown to be liver failure, followed by hepatocellular carcinoma, as was found in previous studies [8, 12]. The median survival time of all patients who underwent endoscopic obliteration for GV bleeding was 5.5 years, and the 1-year, 10-year, and 15-year cumulative survival rates of such patients were 76%, 28%, and 12%, respectively.

The overall safety of Histoacryl injection is generally good [5–11]. The injection of an excessive amount of Histoacryl can result in the migration of the injected material after intravasal injections and local tissue necrosis after paravasal injections. Histoacryl should be diluted with 5% Lipiodol (1:1) to lengthen the Histoacryl polymer and allow fluoroscopic monitoring of the intravariceal injections and the extent of the occlusion induced by the injected Histoacryl. The amount of Histoacryl injected should be based on the amount required to fill the GV. If the Histoacryl mixture alone is used to fill the GV, then a large amount of the mixture will be required. As Histoacryl diluted with Lipiodol does not polymerize immediately on contact with blood, the subsequent injection of 50% glucose could help to spread the Histoacryl mixture, which would reduce the amount of Histoacryl required to obstruct the GV. After the injection of 50% glucose, the Histoacryl mixture induces complete vascular obliteration.

To avoid complications, the speed of the Histoacryl injection is important. A slow rate of injection can result in the Histoacryl mixture being displaced by blood flow before it has polymerized in the GV. Thus, rapid injections are recommended, especially in cases involving GV of greater than 10 mm in diameter [11, 13]. However, the subsequent injection of the 50% glucose should be conducted slowly as injecting it rapidly would increase the risk of the Histoacryl mixture being pushed out from the GV and into the inflow/outflow varicose vein, which is known as ectopic embolization. In previous studies, the leakage of a large amount of Histoacryl into muscular tissue caused severe complications, such as gastric wall necrosis and retroperitoneal abscesses. These complications were refractory to conservative treatment and needed to be treated surgically to prevent them from becoming life-threatening [11, 13]. To avoid severe complications developing, accurate intravariceal injections of Histoacryl should be administered at few puncture sites. In addition, the fluoroscopic monitoring of the injection process is very important for reducing the risk of complications and ensuring that GV are completely obliterated.

In conclusion, the complete endoscopic obliteration of GV with Histoacryl under fluoroscopic guidance can rapidly save patients from life-threatening GV bleeding and remove patients' long-term fears regarding the risk of recurrent bleeding. Assessments of variceal anatomy can provide clinically useful information that might aid the development of improved treatment strategies for the patients with GV.

References

1. Watanabe K, Kimura K, Matsutani E, et al. Portal hemodynamics in patients with gastric varices. A study in 230 patients with esophageal and/or gastric varices using portal vein catheterization. Gastroenterology. 1988;95:434–40.
2. Iwase H, Suga S, Schimada M, et al. Eleven-year survey and efficacy of endoscopic injection sclerotherapy using 2% sodium tetradecyl sulfate and contrast medium. J Clin Gastroenterol. 1996;22:58–65.
3. Hon MC, Lin HC, Kuo BIT, et al. The rebleeding course and long-term outcome of esophageal variceal hemorrhage after ligation: comparison with sclerotherapy. Scand J Gastroenterol. 1999;11:1071–6.
4. Goff JS. Endoscopic sclerotherapy for esophageal and gastric varices: safety and efficacy. Endoscopy. 1994;26:483–5.
5. Stiegmn GV. Elastic band ligation of esophageal and gastric varices. Advanced therapeutic endoscopy. New York: Raven Press; 1994. p. 95–103.
6. Soehendra N, Nam VC, Grimn H, et al. Endoscopic obliteration of large oesophageal gastric varices with bucrylate. Endoscopy. 1986;18:25–6.
7. Kind R, Gugkielmn A, Rodella L, et al. Bucrylate treatment of bleeding gastric varices: a 12 year's experience. Endoscopy. 2000;32:512–9.
8. Huang YH, Yeh HZ, Chen GH, et al. Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacryl) injection: long-term efficacy and safety. Gastrointest Endosc. 2000;52:160–7.
9. Iwase H, Suga S, Morise K, et al. Color Doppler endoscopic sonography for the evaluation of gastric varices and endoscopic obliteration with cyanoacrylate glue. Gastrointest Endsc. 1995;41:150–4.
10. Iwase H, Maeda O, Shimada M, et al. Endoscopic ablation with cyanoacrylate glue for isolated gastric variceal bleeding. Gastrointest Endsc. 2001;53:585–92.
11. Iwase H, Shimada M, Tsuzuki T, et al. Long-term results of endoscopic obliteration with cyanoacrylate glue for gastric fundal variceal bleeding: a 17-year experience. JJPH. 2011;17:137–44.
12. Kind R, Gugkielmn A, Rodella L, et al. Bucrylate treatment of bleeding gastric varices: a year' experience. Endoscopy. 2000;32:512–9.
13. Seewald S, Stiram PVJ, Naga M, et al. Cyanoacrylate glue in gastric variceal bleeding. Endoscopy. 2002;34:926–32.

Chapter 35
Endoscopic Treatment of Gastric Varices: α-Cyanoacrylate Monomer Method

Katsutoshi Obara

Abstract Massive bleeding from gastric varices is a life-threatening event requiring immediate hemostatic measures, which is not easy to predict. However, as large bulging varices and those exhibiting signs of erosion or red color signs are at particularly high risk of bleeding, such varices should be treated proactively even where there is no history of bleeding. For the treatment of bleeding gastric varices, injection of α-cyanoacrylate monomer (αCA) has been performed in Japan as a safe and effective procedure because of its significant hemostatic effect. However, as rebleeding often occurs after the initial bleeding has been stopped with αCA injection, the application of an elective treatment is important. To prevent recurrence after elective or prophylactic treatment, it is essential to obliterate not only the varices but also their blood supply routes by means of αCA-ethanolamine oleate combination therapy, where endoscopic ultrasonography and three-dimensional computed tomography play important roles in the preprocedural study of portal hemodynamics and in the postprocedural evaluation of the outcomes. Furthermore, application of the consolidation method is essential to further reduce recurrence over an extended period.

Keywords Gastric varices · α-Cyanoacrylate monomer · αCA method · αCA-EO combination method · Consolidation method (mucosal fibrosis method)

35.1 Introduction

Cyanoacrylate (CA) adhesives were originally used as surgical adhesives for the closure of wounds on blood vessels and organs. In 1986, Soehendra et al. [1] applied *n*-butyl-2-cyanoacrylate (Histoacryl Blue®: HA) as an endoscopically administered

K. Obara
Department of Advanced Gastrointestinal Endoscopy, Fukushima Medical University, Fukushima, Fukushima, Japan
e-mail: k-obara@fmu.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_35

embolic agent in bleeding cases of gastric varices. Since then, HA has been used on refractory gastric varices that cannot be cured with ethanolamine oleate (EO). In Japan, Suzuki et al. [2] used HA in 1988, and Obara et al. [3] used α-cyanoacrylate monomer (Aron α-A®: αCA) in 1989. Both reported that CA adhesives were highly effective for use on refractory gastric varices.

While more reports exist on HA than on αCA, the two treatments produce comparable results, with hemostasis rates over 90% and rebleeding rates below 15% [4–7]. Based on the published literature, Fukui et al. established the *Evidence-Based Clinical Practice Guidelines for Liver Cirrhosis in 2015*, in which the injection of cyanoacrylate is recommended for the management of bleeding gastric varices because it is more effective than beta-blocker medication or endoscopic variceal ligation (EVL) alone (evidence level A, strength 1) [8].

This chapter describes the treatment of gastric varices using the αCA method.

35.2 Action Mechanism of αCA

When **α**CA is injected into a blood vessel and comes into contact with blood, it is instantaneously polymerized and physically obliterates the intravascular lumen, blocking the blood flow. Unlike EO, it does not form a thrombus damaging the vascular endothelial cells. The local retention property was studied at the author's institute by injecting solutions of **α**CA and Lipiodol® at various concentrations into the cephalic veins of adult mongrel dogs [3, 9]. The **α**CA moved easily in the blood vessel when the concentration was 30% or lower, retention was uncertain at 40%, and retention in the injected area was assured when the concentration was 50% or higher. At 80% or higher, injection was difficult as the solution was prone to hardening inside the catheter before reaching inside the varices. For reasons of safety, therefore, 60–75% should be the optimum concentration in actual clinical practice. As **α**CA is regarded as foreign matter by the living body, in most cases, excretion of **α**CA into the stomach 6 months to 1 year after injection results in a flattening of variceal morphology (Fig. 35.1).

35.3 Indications

Treatment using the **α**CA method is absolutely indicated for bleeding cases and elective cases. If the patient's general physical condition is good and endoscopic treatment is applicable, perform the treatment using the **α**CA method. If endoscopic treatment is not applicable due to the patient's poor general physical condition or if the quality of the endoscopic image is poor due to massive bleeding, perform temporary hemostasis by means of a balloon tamponade until the **α**CA method is applicable. According to the nationwide cohort study by Murashima et al. in 2009 [6, 10], 19.2% of the 388 bleeding cases of gastric varices at 31 institutes in Japan were treated with αCA, 31.3% with HA, 13.3% with balloon-occluded retrograde

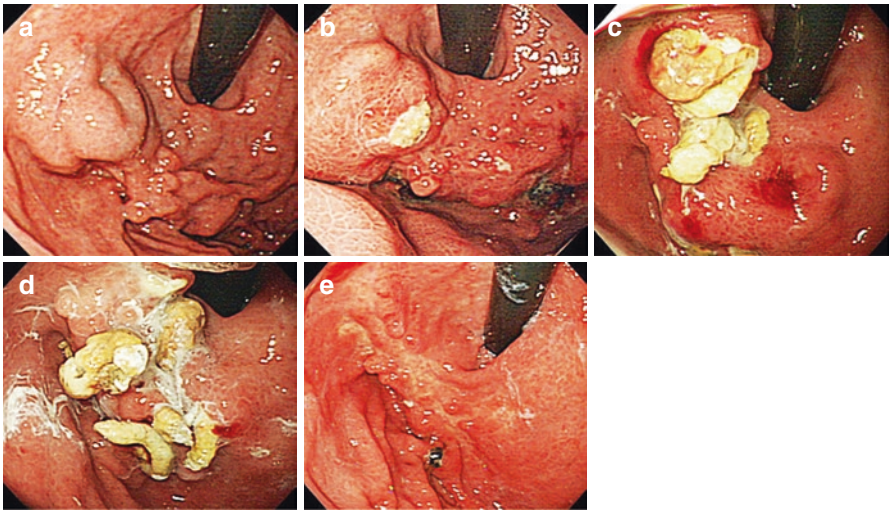


Fig. 35.1 Morphology of gastric varices before and after αCA-EO combination therapy. (**a**) Before treatment. (**b**) After 1 week. (**c**) After 3 months. (**d**) After 6 months. (**e**) After 12 months. *αCA* α-cyanoacrylate, *EO* ethanolamine oleate

transvenous obliteration (B-RTO), 10.7% with EVL, and 10.1% with balloon tamponade (B-RTO seems to have been applied after hemostasis).

Kim et al. [11] reported in a prospective study on 117 patients with gastric fundal varices that the cumulative bleeding rates at 1, 3, and 5 years were 16%, 36%, and 44%, respectively. They also investigated risk factors for bleeding from gastric fundal varices and reported that large variceal size, the presence of red color (RC) signs, and hepatic functional reserve were significant independent prognostic factors for bleeding. In Japan, prophylactic treatment is indicated for cases where an RC sign, erosion, or ulceration on varices is observed, in cases of large expanded varices (F2-3) [12, 13] where a tendency toward rapid growth is observed or where the gastric varices remain or reform after endoscopic treatment of the esophageal varices [14].

35.4 Case Reports

35.4.1 Bleeding Cases

If the patient is in hemorrhagic shock, prioritize shock countermeasures. Once the respiratory and circulatory systems have been stabilized, immediately proceed to emergency endoscopy.

If the patient is not in hemorrhagic shock, perform the αCA method under fluoroscopy [8]. If bleeding gastric varices are discovered during emergency endoscopy in the endoscopy suite, apply temporary hemostasis by means of a balloon tamponade, and move the patient to the fluoroscopy room. If this is not possible, it may be

necessary to perform the αCA method without fluoroscopy in the endoscopy suite. The recommended dilution concentration to minimize the risk of the agent flowing into the general circulation and maximize the needle's ease of passage is 70–80% with HA and 60–75% with αCA [5, 14].

At our institute, 75% αCA is used for bleeding cases. After suctioning 0.6 mL of Lipiodol® in a 2.5 mL syringe, suction 1.8 mL of αCA to prepare 2.4 mL of 75% αCA solution. Be sure to mix it thoroughly before injection. Then, insert the endoscope and observe the morphology of the varices and the bleeding point. Change the patient's position to the supine position immediately before puncturing the varices, and insert a 20G or 21G puncture needle in the vicinity of the bleeding point. Confirm the blood reflux, flush the blood inside the puncture needle with a contrast agent, and then inject the 75% αCA at once. The bleeding will stop immediately. If a massive blood clot obscures the field of view, change the patient's position to the right lateral and head-up tilt position to move a clot toward the vestibular part to ensure the field of view. After αCA injection, confirm the injected area using fluoroscopy. At this point, if the contrast imaging results of the varices or the blood supply routes are inadequate, this means the blood is still flowing too quickly. To deal with this, inject αCA again until good contrast imaging results are obtained, and perform EO injection to obliterate the blood supply routes. In cases with severe hepatic disorder or a poor general physical condition, stop the treatment after injecting a sufficient amount of αCA into the varices, and wait for an improvement in the patient's general physical condition so that the αCA-EO combination method can be applied electively at a later date [15].

35.4.2 Elective/Prophylactic Cases

The most common elective and prophylactic treatments for gastric varices with a high risk of bleeding are the CA method and B-RTO [8, 16]. Which treatment is used depends on the policy of each institute; however, as the CA method preserves the gastrorenal (GR) shunt, it has an advantage over B-RTO in that it requires less EO and has lower esophageal varices emergence rate after treatment.

Most of the isolated gastric varices present endoscopic findings of fundal varices (Lg-f) or cardio-fundal varices (Lg-cf) [12, 13]. They present different hemodynamics and require customized treatment techniques because the blood supply route for Lg-f is the short gastric vein (SGV) or the posterior gastric vein (PGV), while those for Lg-cf are the SGV, the PGV, and the left gastric vein in most of the cases. These hemodynamic findings can be identified with endoscopic ultrasonography (EUS) and three-dimensional computed tomography (3D-CT) before treatment. The αCA-EO combination therapy is performed under fluoroscopy. First, inject αCA into the varices to obliterate them and block the blood flow, and next, puncture the blood supply route side of the varices and obliterate the blood supply routes by EO injection. This combination therapy can achieve total obliteration of both the gastric varices and their blood supply routes (Fig. 35.2).

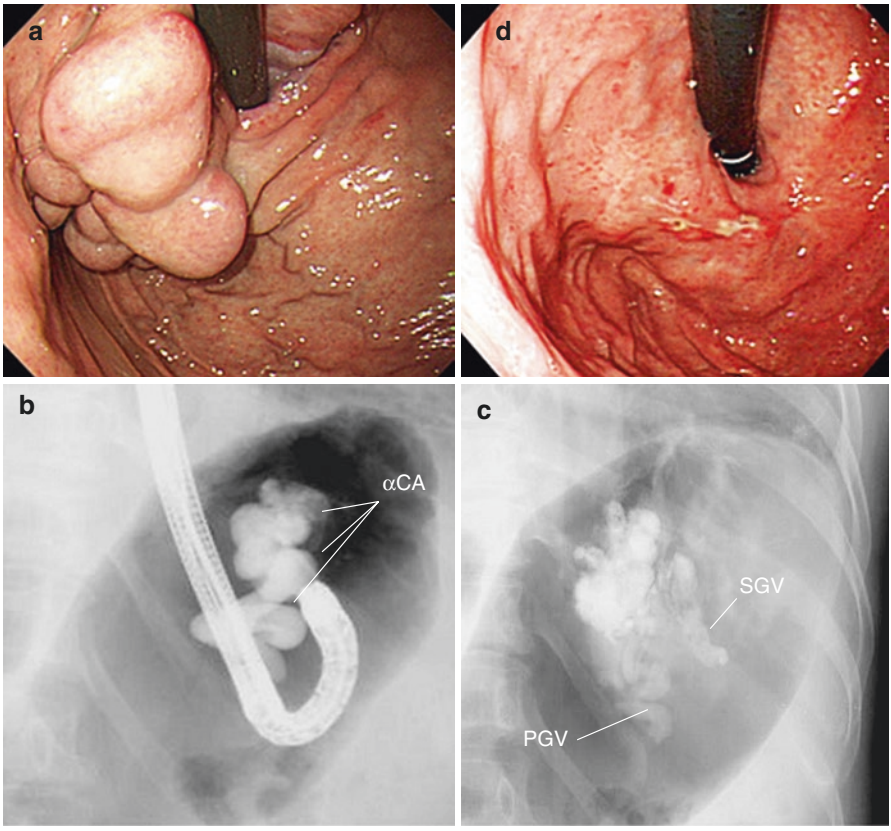


Fig. 35.2 Treatment of cardio-fundal varices. (**a**) Preprocedural endoscopic findings: Lg-cf, F2. (**b**) αCA method: Inject 1.4 mL of 62.5% αCA at 3 points on the gastric varices. (**c**) EO method: Inject EO into the blood supply routes (SGV and PGV) to complete the treatment. (**d**) Endoscopic image 3 years after treatment: No gastric varices were observed. *αCA* α-cyanoacrylate, *EO* ethanolamine oleate, *SGV* short gastric vein, *PGV* posterior gastric vein

35.5 Selection of Treatment Method Based on Contrast Imaging and EUS Findings

As Imamura et al. [15] reported that a strong correlation ($p < 0.01$) was observed between the diameters of gastric varices and their blood flow volume irrespective of the location, identification of the variceal diameters is essential to the selection of an optimal treatment method. The diameters of gastric varices cannot be estimated from the endoscopic findings alone; therefore, variceal contrast imaging and EUS are critical. In the following paragraph, the selection of the treatment method is described based on the diameters of gastric varices (Fig. 35.3).

In cases where the diameter is less than 5 mm, select the sclerosant to be used based on the findings of the contrast imaging. Specifically, if the contrast imaging

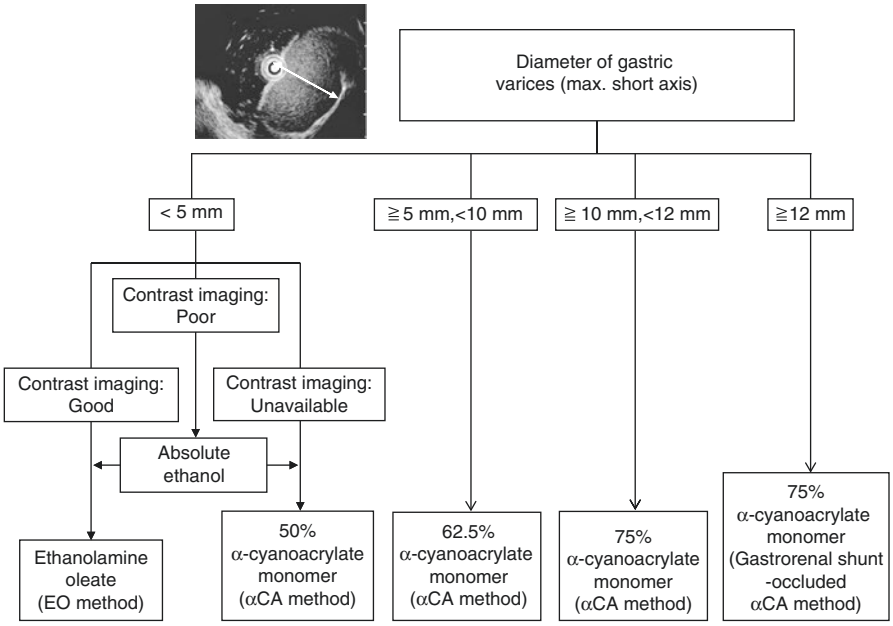


Fig. 35.3 Selection of treatment method based on the diameter of gastric varices measured with endoscopic ultrasonography

result is good, the varices can be treated by means of the EO method. If the contrast imaging is poor, inject ET 1 mL at a time intermittently (up to a total of 3 mL). Wait 1–2 min, and attempt contrast imaging after each injection. Once you get a good result of the contrast imaging, perform the EO method. If the contrast imaging is still poor, apply the αCA method using 50% αCA. If the first contrast imaging result is unavailable, select the αCA method using 50% αCA from the beginning. Where the diameter of the varices is 5 mm or greater and less than 10 mm, use 62.5% αCA. Where it is 10 mm or greater and less than 12 mm, use 75% αCA. In either case, administer αCA in a dose of 2 mL or less per injection. In cases where the diameter is 12 mm or greater, the risk of deviation from the GR shunt into the general circulation is high, which could lead to a pulmonary or cerebral embolism. Therefore, the shunt-occluded CA method in which the GR shunt is occluded with a B-RTO balloon catheter to block or reduce blood flow and the 75% αCA is injected endoscopically is recommended as the safest, most effective treatment method [17].

35.6 Evaluation of the Complete Obliteration

Since the αCA method maintains the variceal morphology for some time after treatment, the obliteration condition cannot be assessed with endoscopy. One simple way to judge the condition involves puncturing the varices and checking for the

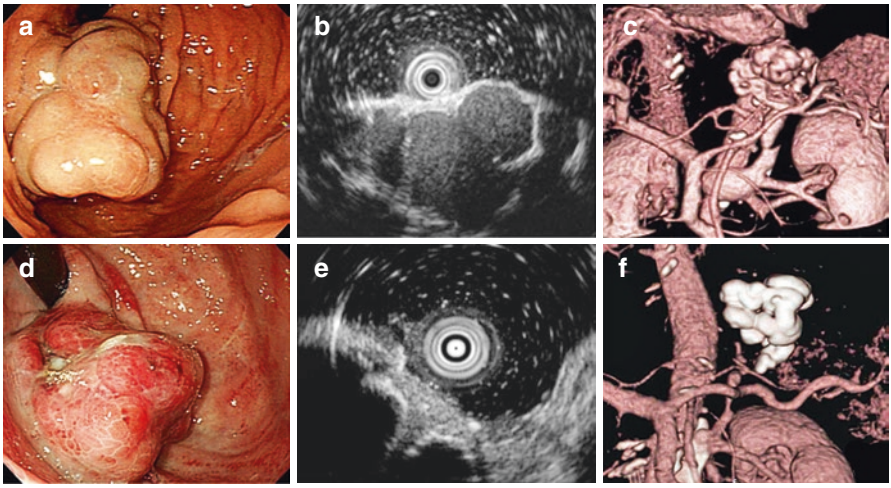


Fig. 35.4 Evaluation of αCA-EO combination therapy. (**a**–**c**) Preprocedural images. (**a**) Endoscopic findings: Lg-cf, F3, RC1. (**b**) EUS findings: Gastric varices were observed as non-echoic lumen images. (**c**) 3D-CT findings: The blood supply routes were the SGV and PGV, and the drainage route is the gastrorenal shunt. (**d**–**f**) Images 1 week after treatment. (**d**) Endoscopic findings: Lg-cf, F3-Th, RC0, UI. (**e**) EUS findings: Varices were observed as high-echoic images accompanied by acoustic shades. No residual lumen was observed in the gastric wall. (**f**) 3D-CT findings 1 week after treatment: αCA polymer in the varices was observed in white and the blood supply routes have been eliminated, which demonstrates complete obliteration. *αCA* α-cyanoacrylate, *EO* ethanolamine oleate, *EUS* endoscopic ultrasonography, *SGV* short gastric vein, *PGV* posterior gastric vein, *3D-CT* three-dimensional computed tomography

presence/absence of a blood reflux. However, there is a high possibility that small blood vessels will be missed. In such a case, EUS is useful for confirming the presence of residual small vessels in the wall which means confirming whether complete obliteration has been achieved. The αCA-injected areas present echoic images like calculi (strong echo images accompanied by acoustic shadows). Around these areas, non-echoic or low-echoic lumen images (residual vessels) should be searched for. If such images are found, additional treatment should be performed to achieve complete obliteration. Meanwhile, 3D-CT is useful for judging the obliteration of the blood supply routes (Fig. 35.4). Thus, complete obliteration should be confirmed, which means the obliteration of both gastric varices and their blood supply routes.

35.7 Treatment Outcomes

In the years 2000 and 2007, the Endoscopic Pathophysiological Study Group for Treatment of Esophageal and Gastric Varices (Chief Organizer: Katsutoshi Obara), which was attached to the Japan Gastroenterological Endoscopy Society (JGES), played a leading role in conducting large-scale surveys to identify the status of the use of the CA method in the treatment of gastric varices in Japan.

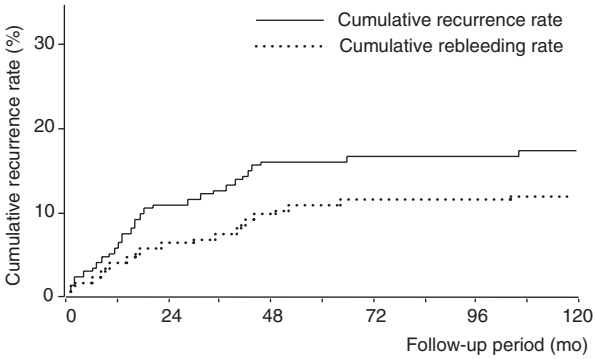


Fig. 35.5 Cumulative recurrence and rebleeding rates with the αCA-EO combination therapy. Modified from: Wakatsuki T. Obara K. Analysis of prognostic factors in patients with gastric varices after endoscopic treatment. Dig Endosc. 2009;21:232–238. *αCA* α-cyanoacrylate, *EO* ethanolamine oleate

In the 2000 survey, 302 αCA and 737 HA cases treated at 38 institutes between 1988 and 1997 were registered, and their hemostasis rates were 93% and 95%, respectively. Complication rates were 5.0% in αCA (pulmonary embolism, 1; outflow to the left renal vein, 1; outflow to the inferior vena cava, 1; variceal bleeding, 7) and 8.1% in HA (pulmonary embolism, 4; flow to the portal vein, 3; splenic embolism, 1; hematothorax, 1; variceal bleeding, 48). Mortality rates were 1.0% in αCA (gastric variceal bleeding, 3) and 1.4% in HA (gastric variceal bleeding, 7; esophageal variceal bleeding, 3), where the causes of death included the endoscopists' insufficient skill in achieving hemostasis and the poor general condition of the patients. No other severe complications were reported. In the 2007 survey, 121 αCA and 274 HA cases treated at the 17 institutes between 2003 and 2007 were registered, and their hemostasis rates were 97.5% and 97.8%, respectively, with both rates representing increases compared with those in the 2000 survey. Complication rates were 3.0% in αCA and 3.8% in HA, and mortality rates were 0.2% in αCA and 0.4% in HA, with both rates representing decreases compared with those in the 2000 survey [6].

Wakatsuki et al. [5] retrospectively studied 115 patients with gastric varices (19 emergency, 18 elective, and 83 prophylactic cases) treated using the αCA-EO combination method between October 1988 and December 2003. They reported that gastric variceal bleeding was well-controlled in all the cases with αCA injection and no early rebleeding was observed after αCA-EO combination therapy. They also reported that all the gastric varices were completely obliterated with 3.4 ± 2.5 treatment sessions and the cumulative recurrence rates at 1, 3, and 5 years after the αCA-EO combination method were 7.0%, 15.6%, and 20.0%, respectively, while the cumulative bleeding recurrence rates were 3.5%, 8.7%, and 14.8%, respectively. Furthermore, most of the recurrent bleeding cases were not severe and could be controlled with repeated injection of αCA (Fig. 35.5).

35.8 Complications of the αCA Method

Complications associated with the αCA method include pulmonary embolism, outflow to the left renal vein [18], outflow to the inferior vena cava, and variceal bleeding according to the survey in 2000 and 2007, while no severe complications were

reported resulting from the αCA method itself [6]. Wakatsuki et al. [5] reported the following complications: bleeding between treatment sessions in four patients (3.5%), pulmonary embolism caused by αCA leakage in three (2.6%), high fever in one (0.9%), and gastric perforation in one (0.9%). In all four patients who experienced bleeding between treatment sessions, the bleeding was stopped by another single treatment session using αCA. As the three patients with pulmonary embolism confirmed by computed tomography were asymptomatic, they received no further treatment outside of their routine follow-up appointments. EUS revealed that the maximum minor axis of the gastric varices was over 12 mm in all the cases of pulmonary embolism. Antipyretic was prescribed once to a patient with high fever, which reduced his temperature back to normal. The gastric perforation healed spontaneously with fasting, intravenous nutrition, and administration of antibiotics and a proton pump inhibitor. There were no fatalities.

35.9 Consolidation Method

For further reduction of the recurrence rates of gastric varices after treatment using the αCA-EO combination method, application of the argon plasma coagulation (APC) consolidation (mucosal fibrosis using APC) is indicated where small veins and perforating veins remain in the gastric wall and gastric extramural blood vessels have developed. With recurrent cases, this method is also indicated where small blood vessels grow in dense clusters, making intravenous injection difficult [14, 19].

After completion of the initial αCA-EO combination method, inject aethoxysklerol (AS) into the mucosa in the periphery of the αCA-injected area. Inject 2–3 mL per injection (for a total dose of 40 mL or less), which will allow the αCA polymer that had formed a template in the gastric varices to fall off inside the stomach. Following this, apply APC concentrically in the region from the cardia to the fundus while avoiding the ulcers formed by the AS method. The goal of this treatment is to eliminate any small varices and produce fibrosis of the gastric mucosa and submucosa (Fig. 35.6). EUS observation after application of APC shows thick-

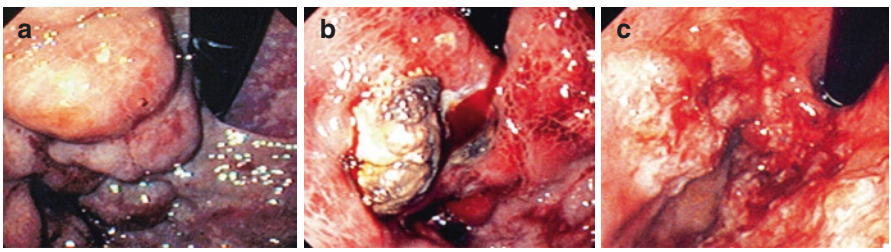


Fig. 35.6 αCA-EO combination method followed by APC consolidation. (**a**) The gastric varices and all the blood supply routes are obliterated with the αCA-EO combination method. (**b**) After application of the αCA-EO combination therapy, paravariceal injection of aethoxysklerol is performed in the mucosa around the gastric varices to force the αCA polymer to fall off. (**c**) After the αCA polymer falls off, the entire region from the cardia to the fundus is eradicated by APC consolidation. *αCA* α-cyanoacrylate, *EO* ethanolamine oleate, *APC* argon plasma coagulation

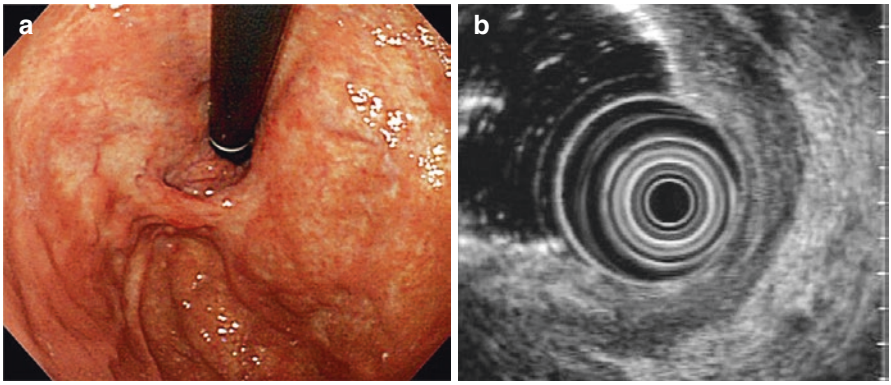


Fig. 35.7 Endoscopic and EUS images after APC consolidation. (**a**) Endoscopy 3 years after APC consolidation therapy of gastric varices found no morphology of the gastric varices at all, nor any sign of recurrence. (**b**) EUS observation showed that the mucosa and submucosa had thickened and no longer had any structure. No lumen image indicating the potential for recurrence was found in the wall. *EUS* endoscopic ultrasonography, *APC* argon plasma coagulation

ening of the mucosa and submucosa (Fig. 35.7). At this time, decide whether additional treatment is required by checking the residual lumina using EUS.

35.10 Conclusion

Since αCA was first introduced in Japan, it has been used at some institutes for the treatment of bleeding gastric varices because of its significant hemostatic effect. For elective and prophylactic cases, the αCA-EO combination method has been used to successfully obliterate both gastric varices and their blood supply routes resulting in effective prevention of variceal recurrence and initial bleeding or rebleeding. Furthermore, APC consolidation has also been applied at some institutes to further reduce recurrence of gastric varices. These therapies should be performed taking the patient's condition, portal hemodynamics, and quality of life fully into consideration.

References

1. Soehendra N, Nam VC, Grimm H, Kempenneers I. Endoscopic obliteration of large esophagogastric varices with bucrylate. Endoscopy. 1986;18:25–6.
2. Suzuki H, Ymamoto M, Chibai M, et al. Sclerotherapy of gastric varices with histoacryl. Prog Dig Endosc. 1988;33:83–6. [In Japanese].
3. Obara K, Ohira H, Sakamoto H, Iwasaki K, Mitsuhashi H, Suzuki S, et al. Endoscopic injection sclerotherapy with α-cyanoacrylate monomer for emergent bleeding from isolated gastric varices: report of 3 cases. Gastroenterol Endosc. 1989;31:3209–16. [In Japanese with English abstract].

4. Garcia-Pagan JC, Barrufet M, Cardenas A, Escorsell A. Management of gastric varices. Clin Gastroenterol Heapatol. 2014;12:919–28.
5. Wakatsuki T, Obara K, Irisawa A, Sakamoto H, Kuwana T, Takiguchi F, et al. Analysis of prognostic factors in patients with gastric varices after endoscopic treatment. Dig Endosc. 2009;21:232–8.
6. Obara K. National survey on the αCA method for gastric varices. In: Endoscopic treatment of esophagogastric varices. Tokyo: NARUNIA; 2016. p. 71–7.
7. Imai Y, Nakazawa M, Chikayama T, Watanabe K, Ando S, Mizuno Y, et al. Results of endoscopic treatment of bleeding gastric fundic varices by cyanoacrylate injection and additional treatment. Nihon Monmyakuatsu Koshinsho Gakkai Zsshi (Jpn J Portal Hypertens). 2012;18:36–9. [In Japanese].
8. Fukui H, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51:629–50. https://doi.org/10.1007/s00535-016-1216-y.
9. Obara K, Endoscopic GV. Treatment. In: Endoscopic treatment of esophagogastric varices. Tokyo: NARUNIA; 2016. p. 10–4.
10. Murashima N, Watanabe N, Ohta M, Obara K, Oho K, Kokubu S, et al. Evaluation of the therapies for bleeding gastric varices in Japan: a retrospective multi-center cohort study. Nihon Monmyakuatsu Koshinsho Gakkai Zsshi (Jpn J Portal Hypertens). 2010;16:88–103. [In Japanese].
11. Kim T, Shijo H, Kokawa H, Tokumitsu H, Kubara K, Akiyoshi N, et al. Risk factors for hemorrhage from gastric fundal varices. Hepatology. 1997;25:307–12.
12. Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc. 2010;22:1–9. https://doi.org/10.1111/j.1443-1661.2009.00929.x.
13. The Japan Society for Portal Hypertension. The general rules for study of portal hypertension. 3rd ed. Tokyo, Kanehara & Co., Ltd; 2013. [In Japanese].
14. Obara K, Toyonaga A, Kokubu S. Guidelines for the endoscopic treatment of esophagogastric varices. In: Society for Japanese Gastroenterological Endoscopy, editor. Guidelines for gastrointestinal endoscopy. 3rd ed. Tokyo: Igaku-Shoin; 2006. p. 215–34. [In Japanese].
15. Imamura H, Irisawa A, Shibukawa G, Takagi T, Hikichi T, Obara K, et al. Echo-endoscopic analysis of variceal hemodynamics in patient with isolated gastric varices. Endosc Ultrasound. 2014;3:238–44. https://doi.org/10.4103/2303-9027.144542.
16. Kanagawa H, Mima S, Kouyama H, Gotoh K, Uchida T, Okuda K. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. J Gastroenterol Hepatol. 1996;11:51–8.
17. Imazu H, Matsui T, Kobayasi Y, Noguchi R, Miyamoto Y, Kawata M, et al. Balloon catheter-assisted endoscopic sclerotherapy for gastric fundal varices using alpha-cyanoacrylate monomer. J Clin Gastroenterol. 2001;33:49–52.
18. Irisawa A, Obara K, Sato Y, Saito A, Orikasa H, Ohira H, et al. Adherence of cyanoacrylate which leaked from gastric varices to the left renal vein during endoscopic injection sclerotherapy: a histopathologic study. Endoscopy. 2000;32:804–6.
19. Obara K, Endoscopic GV. Treatment. In: Endoscopic treatment of esophagogastric varices. Tokyo: NARUNIA; 2016. p. 46–71.

Chapter 36
Endoscopic Treatment of Gastric Varices: Indwelling Snare Method

Tomoharu Yoshida, Yasuyuki Shirai, Koji Aoyama, and Syunnsuke Itoh

Abstract The authors have been performing endoscopic treatment using a detachable snare in combination with sclerotherapy to treat solitary gastric varices. This chapter reports on the effectiveness of this treatment with respect to gastric varices through a discussion of the applications of endoscopic variceal ligations (EVLs) using a detachable snare and simultaneous endoscopic injection sclerotherapy and ligation (EISL), procedures, treatment performance, and prognosis.

Keywords Endoscopic treatment · Gastric varices · Detachable snare · EISL · EVLs + EISL

36.1 Introduction

We have been performing endoscopic gastric variceal ligation using a detachable snare that opens to a diameter of 4 cm (EVLs) as a modification of endoscopic variceal ligation (EVL) since June 1992. However, due to the high rate of recurrence after EVLs, endoscopic injection sclerotherapy and ligation (EISL) have been carried out concurrently with EVLs since March 1995 [1].

Here we describe our EVLs + EISL method and report on the results of a prospective study conducted to investigate its value.

T. Yoshida (✉) · Y. Shirai · K. Aoyama · S. Itoh
Department of Gastroenterology and Hepatology, Kokura Memorial Hospital, Kitakyushu, Fukuoka, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_36

36.2 Indications

According to the Japanese gastrointestinal endoscopy guidelines [2], prophylactic treatment applications include:

- Symptoms accompanying erythema found proximal to a gastric varix
- Erosion or ulceration accompanying a gastric varix
- Rapidly expanding gastric varices
- F2 and F3 engorged gastric varices or remaining gastric varices after esophageal varices treatment or newly formed varices

Both cases involving emergent hemorrhaging of solitary gastric varices and cases with a prior history of bleeding were indications for this treatment method [3].

36.3 Treatment Procedure

A schematic diagram of the procedure is displayed in Fig. 36.1. For EVL, by using a two-channel endoscope (GIF 2T260 and GIF 2T240), ligate the gastric varices with the loop of the detachable snare while gripping the edge of the varices with V-shaped alligator forceps. After completing the ligation by applying 2–3 kg of pressure by using the grip handle, confirm that the ligated gastric varices are changing color to purple or white after approximately 1 min, and then place the loop.

For the subsequent EISL procedure [4, 5], by using a typical direct-view endoscope (one channel) with the overtube placed, conduct sclerotherapy to treat the remaining gastric varices proximal to the ligation site by using ethanolamine oleate with a contrast agent additionally administered via a 23-G syringe. Perform ligation

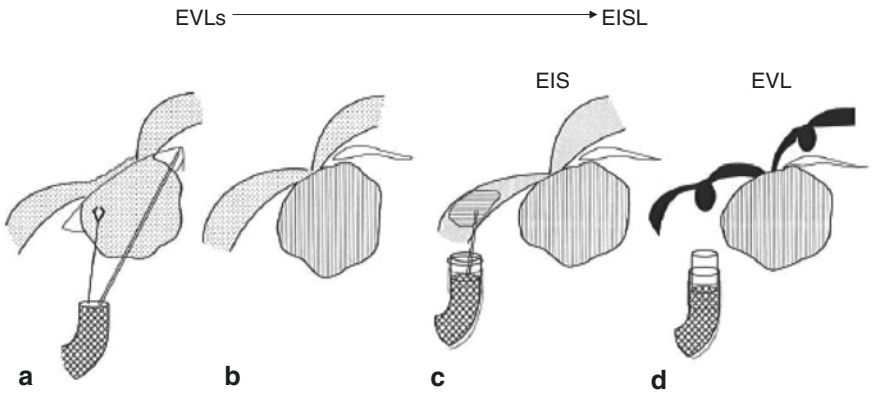


Fig. 36.1 Schematic diagrams of EVLs + EISL (excerpted from Yoshida [1]). (**a**) The unfolded loop is applied to the base of the gastric varices. (**b**) The loop is tightened around the base of the varices (EVLs). (**c**) The residual varices around the ligated portion are sclerosed by injection of ethanolamine oleate with contrast medium. (**d**) The injected varices are ligated by using a pneumo-activated endoscopic variceal ligation device (EISL)

at the needle puncture site by using a pneumo-activated EVL device. Perform additional EISL procedures to address any further suspected remaining varices; after which, the first treatment will be completed.

After the treatment, repeat the EISL procedure every 1 or 2 weeks to address any suspected remaining gastric varices until all varices have disappeared.

Disappearance of gastric varices is defined as disappearance of any varices-like protrusion visible on endoscopy.

In cases involving emergency hemorrhaging, bleeding should first be stopped through EVLs. After assessing the patient's liver function and the hemodynamics in the gastric varices via contrast-enhanced computed tomography, EISL treatment should be performed as soon as possible with the aim of achieving disappearance of the gastric varices. Successful stoppage of emergency hemorrhaging is defined as stoppage achieved through treatment without recurrence for a 1-week period after such stoppage.

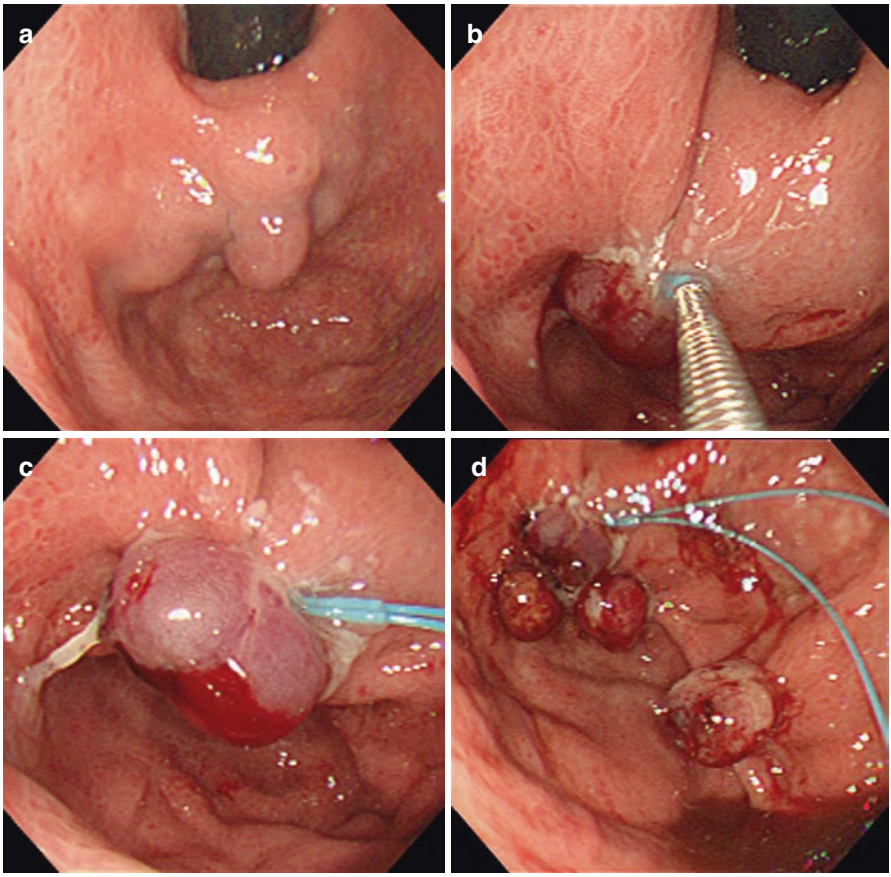


Fig. 36.2 Endoscopic picture of EVLs + EISL. (**a**) Endoscopic view of gastric varices. (**b**) The loop is tightened around the base of the varices (EVLs). (**c**) The loop is detached (EVLs). (**d**) The residual varices around the ligated portion are sclerosed by injection sclerotherapy. The injected varices are ligated by using a pneumo-activated endoscopic variceal ligation device (EISL)

Table 36.1 Treatment performance of EVLs + EISL

Gastric varices' disappearance rate	97.2% (104/107)
Emergency hemostasis rate	95% (19/20)
Postoperative bleeding	5.6% (6/107)
Gastric perforation	0.9% (1/107)
Postoperative mortality due to bleeding	0.9% (1/107)
Mean no. of treatments	2.2 ± 1.3 treatments
Mean treatment time	14 min

After the treatment, patients undergo clinical monitoring with endoscopic examinations conducted every 4–6 months (Fig. 36.2).

36.4 Results and Prognosis

A total of 107 cases were treated via EVLs + EISL. The distribution of these cases is as follows: as prophylactic treatment, 60 cases; as elective treatment, 27 cases; and to address emergency hemorrhaging, 20 cases. The distribution of specific locations of the solitary gastric varices encountered is as follows: Lg-c, 12 cases; Lg-f, 17 cases; and Lg-cf, 78 cases [6]. Regarding hepatic function, 36 cases were designated as Child-Pugh class A; 45 cases, as Child-Pugh class B; and 26 cases, as Child-Pugh class C (Table 36.1).

Disappearance of gastric varices was observed in 97.2% of the cases, and varix shrinkage was observed in all the cases. Bleeding was stopped in 19 (95%) of 20 cases involving emergency hemorrhaging. Postoperative bleeding was observed in six cases (5.6%). Postoperative bleeding-related mortality was confirmed in one case (0.9%). Gastric perforation was found in one case (0.9%) but was resolved through maintenance therapy.

The mean number of treatments was 2.2 ± 1.3, and the mean treatment time was 14 min. For the cumulative recurrence rates, the 1-year recurrence rate was 7%, the 3-year recurrence rate was 22%, and the 5-year recurrence rate was 39%. For the cumulative bleeding rates, the 1-year bleeding rate was 3%, the 3-year bleeding rate was 5%, and the 5-year bleeding rate was 12%. Although changing the shunt from the gastric varices to the left renal vein before and after treatment was considered in 21 cases, the shunt to the renal vein survived in all 21 cases. This treatment is believed to only have the effect of removing varices on the gastric wall interior and has no impact on shunts to the renal vein.

References

1. Yoshida T, Harada T, Shigemitsu T, Takeo Y, Miyazaki S, Okita K. Endoscopic management of gastric varices using a detachable snare and simultaneous endoscopic sclerotherapy and O-ring ligation. J Gastroenterol Hepatol. 1999;14:730–5.
2. Obara K, Toyonaga A, Kokubu S. Guidelines for the endoscopic treatment of esophagogastric varices. In: Society for Japanese Gastroenterological Endoscopy, editor. Guidelines for gastrointestinal endoscopy. 3rd ed. Tokyo: Igaku-Shoin Ltd; 2006. p. 215–34. [In Japanese].
3. Miyazaki H, Ichikawa T, Taura N, Miuma S, Isomoto H, Nakao KL. Endoscopic management of esophagogastric varices in Japan. Ann Transl Med. 2014;2:42.
4. Nishikawa Y, Hosokawa Y, Doi T, Endo H, Tanimizu M, Hyodo I, et al. Simultaneous combination of endoscopic sclerotherapy and endoscopic ligation for esophageal varices. Gastrointest Endosc. 1995;42:358–60.
5. Shigemitsu T, Yoshida T, Harada T, Takeo Y, Saiki Y, Okita K, et al. Endoscopic injection sclerotherapy with ligation versus endoscopic injection sclerotherapy alone in the management of esophageal varices: a prospective randomized trial. Hepato-Gastroenterology. 2000;47:733–7.
6. Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, et al. General rules for recording endoscopic finding a of esophagogastric varices (2nd edition). Dig Endosc. 2010;22(1):1–9.

Chapter 37
Hemodynamics and Treatment of Ectopic Varices

Katsutoshi Obara

Abstract Formerly, the presence of ectopic varices was difficult to discover, and mortality rates tended to be high when they began to bleed. Nowadays, advances in diagnostic modalities have enabled ectopic varices to be discovered more frequently. However, few randomized controlled trials of large case series have been conducted on ectopic varices, and no evidence-based guidelines have been published concerning their management. According to a nationwide questionnaire survey carried out in 1990 in Japan, ectopic varices were observed in 129 (0.7%) out of a total of 18,540 patients with a history of receiving endoscopic injection sclerotherapy for esophageal varices, representing a low prevalence; however, the prevalence increased substantially to 3.8% in our data reviewed in 2013. On the other hand, the percentages of bleeding cases were 57.4% in 1990 and 45.1% in 2010, which were not significantly different. In Japan, the majority of ectopic varices develop following endoscopic treatment of esophagogastric varices, and therefore, practitioners should conduct follow-up examinations taking ectopic varices into consideration so that even bleeding ectopic varices can be treated timely and effectively. Modalities often used to detect ectopic varices in Japan include endoscopy, computed tomography, and (color Doppler) endoscopic ultrasonography, while therapeutic options range from endoscopic treatment to surgical operation as well as interventional radiology and pharmacology.

Keywords Ectopic varices · Portal hypertension · Endoscopic injection sclerotherapy · Endoscopic variceal ligation · Interventional radiology

K. Obara
Department of Advanced Gastrointestinal Endoscopy, Fukushima Medical University, Fukushima, Fukushima, Japan
e-mail: k-obara@fmu.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_37

37.1 Introduction

Esophagogastric varices are often observed as portosystemic collateral pathways in patients with portal hypertension. Moreover, after the treatment of such varices using endoscopic techniques or open surgery, in many cases the obliteration of the blood supply vessels or the adherence of the resected lesions to adjacent structures causes the blood flow to divert, resulting in the formation of ectopic varices in locations other than the esophagogastric region. In Japan, the majority of patients with ectopic varices, and particularly those with rectal varices, have a history of developing esophageal varices and receiving endoscopic therapy for them [1].

Diagnosis of duodenal varices using X-ray fluoroscopy was first reported in 1931 by Alberti [2] in Germany, and in 1968, Nishioka et al. [3] first reported duodenal varices diagnosed using duodenography and splenoportography in patients with gastric varices in Japan. The first report on sigmoid colon varices by Cabot et al. [4] included details of a discussion among nine medical experts struggling over a differential diagnosis on a 55-year-old male patient admitted to their hospital as many as seven times with a variety of complaints. They were finally able to make a diagnosis based on a specimen of the resected sigmoid colon. Since then, a number of diagnostic modalities and treatment methods have been developed and improved, as revealed in reports of nationwide surveys [1, 5, 6] and reviews conducted by individual institutes [7, 8].

The present chapter describes the epidemiology, clinical characteristics, and treatment of ectopic varices in Japan.

37.2 Pathophysiology

37.2.1 Prevalence and Location

According to a nationwide questionnaire survey carried out in 1990 in Japan [5, 6], ectopic varices were observed in 129 (0.7%) out of a total of 18,504 patients with a history of receiving endoscopic injection sclerotherapy (EIS) for esophageal varices, representing a low prevalence; subsequently, however, the prevalence increased substantially. In 2003, Obara et al. [9] reported that the prevalence of ectopic varices was 13 (1.8%) out of 720 patients treated for esophagogastric varices, and in 2009, Sato et al. [7] reported 43 (3.4%) out of 1218 patients treated for esophagogastric varices exhibited ectopic varices. Moreover, in 2013, Obara et al. [8] reported that ectopic varices were observed in 44 (3.8%) of 1149 patients with a history of receiving endoscopic treatment for esophagogastric varices. The following is a breakdown of the locations in which these ectopic varices were observed and the number of cases for each location: the rectum in 20 (45.5%), the duodenum in 13 (29.5%), the bile duct in 7 (15.9%), the small intestine in 2 (4.5%), and the overall large intestinal region in 2 cases (4.5%) (Fig. 37.1 [10]). Furthermore, a nationwide survey in Japan by the Japan Society for Portal Hypertension conducted from 2001 to 2005 reported

173 ectopic varices [1], the locations of which were as follows: the rectum in 77 (44.5%), the duodenum in 57 (32.9%), the small intestine in 11 (6.4%), the anastomotic site in 10 (5.8%), the biliary duct in 8 (4.6%), the colon in 6 (3.5%), the stoma site in 3 (1.7%), and the diaphragm in 1 case (0.6%) (Fig. 37.2). The survey also

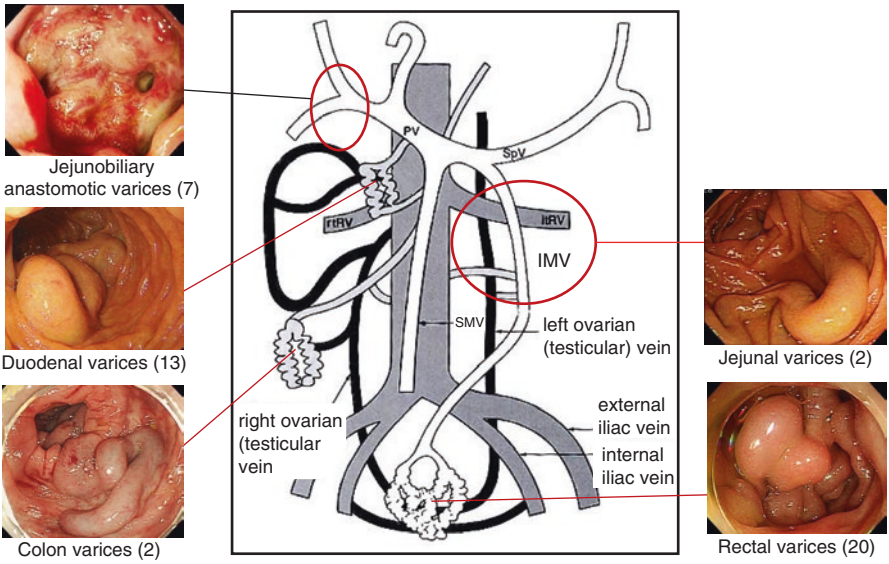


Fig. 37.1 Portosystemic collaterals in 44 patients with ectopic varices at our hospital. *PV* portal vein, *SpV* splenic vein, *rt RV* right renal vein, *lt RV* left renal vein, *IMV* inferior mesenteric vein, *SMV* superior mesenteric vein. Modified from reference [10]

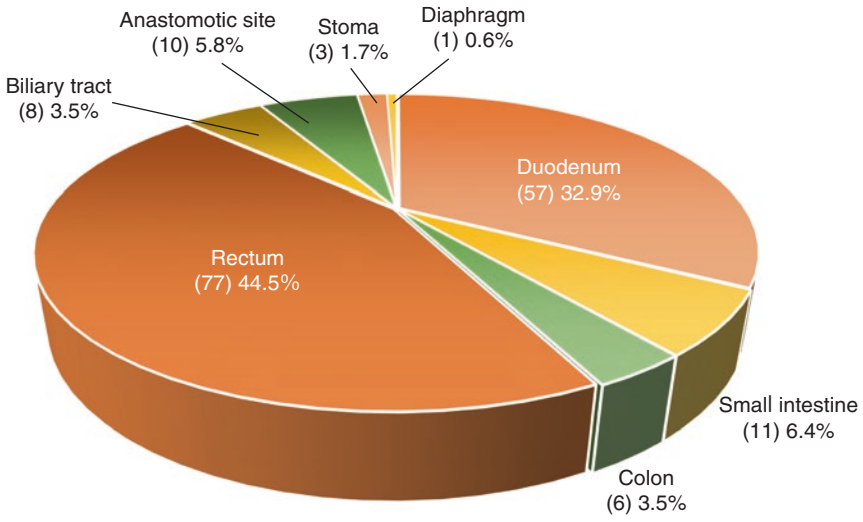


Fig. 37.2 Location of 173 ectopic varices. Quoted from reference [1]

revealed underlying diseases including liver cirrhosis (80.3%), extrahepatic portal vein obstruction (10.4%), and idiopathic portal hypertension (IPH) (4.6%), and as many as 76.9% of all patients with ectopic varices had a history of esophageal varices and 57.9% had received treatment for them.

37.2.2 Bleeding Tendency

In the 1990 questionnaire survey [5, 6], 74 (57.4%) out of 129 cases of ectopic varices were bleeding cases, while the rest were discovered during screening tests. In the 2010 survey [1], 78 (45.1%) out of 173 cases exhibited bleeding, and bleeding rates were not significantly different from those reported in 1990. The bleeding rates according to location were as follows: 100% (3/3) in the stoma site, 81.8% (9/11) in small intestine, 60% (6/10) in anastomosis site, 50% (3/6) in colon, 47.4% (27/57) in duodenum, and 39% (30/77) in rectum. This result indicates that ectopic varices have a strong tendency to bleed regardless of their location. As ectopic varices are often discovered when they are bleeding, initial bleeding rates for nonbleeding cases have not been validated. Furthermore, risk factors for bleeding have yet to be fully studied with controversial reports about red color signs [8, 11, 12]. However, once ectopic varices begin to bleed, mortality rates are high.

37.3 Clinical Characteristics and Treatment

37.3.1 Duodenal Varices

37.3.1.1 Clinical Characteristics

Underlying diseases of duodenal varices in Japan reportedly included liver cirrhosis (80.3%), followed by extrahepatic portal obstruction (EHO) (10.4%) and IPH (4.6%) [1]. Furthermore, Matsui et al. [11] reported in 2008 that the underlying diseases of 12 patients with duodenal varices were liver cirrhosis and pancreatic cancer-related pylemphraxis in 8 and 4 patients, respectively.

The locations in which duodenal varices have been observed in Japan and overseas vary in accordance with the hemodynamics of the underlying diseases. According to a 1990 survey, in countries where EHO is the main underlying disease, the locations of duodenal varices included the duodenal bulb in 72.8% of the cases, while in Japan where liver cirrhosis is the main underlying disease, the descending part accounted for 52.3% of the cases, followed by the duodenal bulb in 38.1% and both locations in 11.1% of the cases [6]. In a 2010 survey, the descending part, the horizontal part, and the duodenal bulb were the locations in 27.2%, 4.6%, and 1.2% cases, respectively. Furthermore, 36 (63.2%) and 20 (35.1%) out of 57 patients with duodenal varices had a history of having developed esophageal varices

and received endoscopic treatment for them, respectively [1]. In addition, in 11 (84.6%) out of 13 bleeding cases, the patients had a history of receiving endoscopic treatment for esophagogastric varices in our data [8].

37.3.1.2 Symptoms and Diagnosis

As hematemesis and melena are major symptoms, duodenal varices are often found during the course of detecting the bleeding source. The presence of duodenal varices should be taken into consideration at the time of the initial diagnosis of gastrointestinal bleeding in patients with portal hypertension, particularly when the patient has a history of endoscopic or surgical treatment of esophagogastric varices.

Endoscopy should be performed in order to thoroughly examine the descending and horizontal parts of the duodenum. When a patient exhibits bleeding from the upper gastrointestinal tract other than the esophagus or stomach, there is a high possibility that duodenal varices are the bleeding source. Accordingly, a further detailed examination should be carried out employing useful modalities to study portal hemodynamics such as endoscopic ultrasound sonography (EUS), three-dimensional computed tomography (3D-CT), color Doppler EUS, and magnetic resonance angiography, among which 3D-CT is particularly important in order to grasp the hemodynamics (Fig. 37.3).

37.3.1.3 Treatment

No clear consensus has been reached on the established treatment method for duodenal varices. However, favorable results have been reported using endoscopic treatment, interventional radiology (IVR), and operative surgery. Treatment strategies should be designed taking into consideration the morphological assessment results and the hemodynamics including the information on the feeding and drainage veins for the varices in question. The main feeding veins for duodenal varices were reportedly the inferior pancreaticoduodenal veins, superior mesenteric veins, duodenal veins, and superior pancreaticoduodenal veins, accounting for 41%, 10.2%, 7.7%, and 7.7% of cases, respectively. Furthermore, it was shown that the main drainage veins were the testicular or ovarian veins, which account for 52.6% of all reported cases [1].

In emergency cases, endoscopic treatment accounted for 85.7%, and in elective cases, endoscopic treatment, IVR treatment, and endoscopic and IVR treatment in combination accounted for 16.6%, 50%, and 16.6% of the cases, respectively. In prophylactic treatment, endoscopic treatment, IVR treatment, and these two in combination accounted for 14.3%, 57.1%, and 28.6% of the cases, respectively. IVR treatment was carried out most frequently in prophylactic and elective cases [1]. Figure 37.4 shows the treatment strategy for ectopic varices at our institute [8]. Seven out of 13 duodenal varices were emergency bleeding cases, and 1 was prophylactic, while the other 5 nonbleeding cases have been observed conservatively.

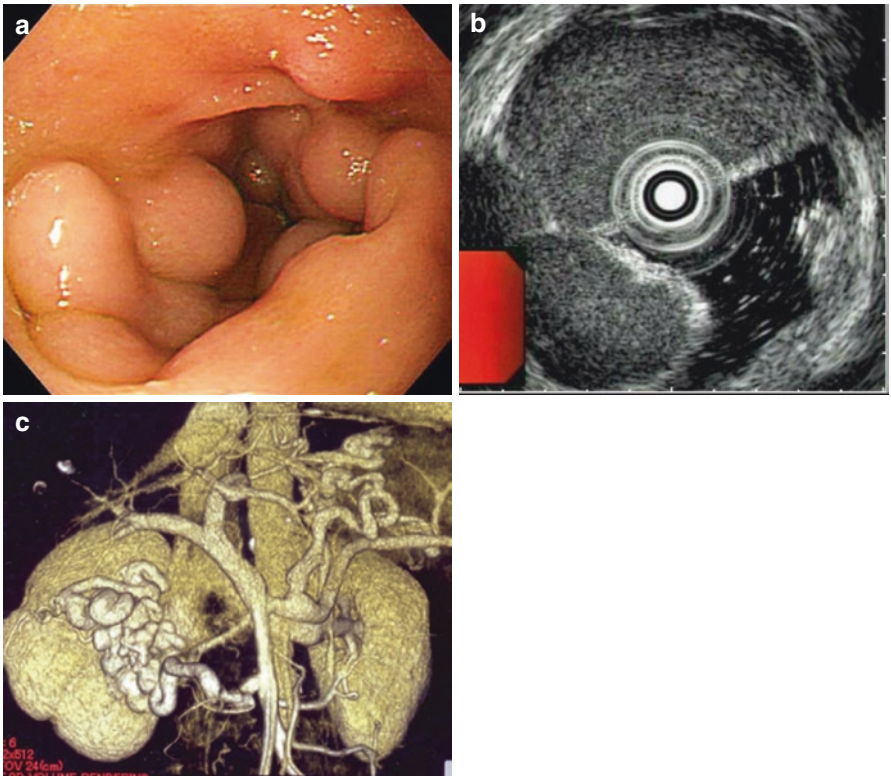


Fig. 37.3 Diagnosis of duodenal varices. Female in her 60s with hepatitis C cirrhosis. (**a**) Endoscopic image showed beaded varices with no red color signs in the descending part of the duodenum. (**b**) EUS using a 20MHs micro probe revealed low echoic lumen in the submucosa. (**c**) The 3D-CT volume rendering method revealed that the feeding vein was the inferior pancreaticoduodenal vein and the drainage vein was the right kidney vein. *EUS* endoscopic ultrasonography, *3D-CT* three-dimensional computed tomography

37.3.1.4 Treatment Techniques

Endoscopic treatments including EIS [13–15], endoscopic variceal ligation (EVL) [16–18], and injection of cyanoacrylate adhesives [19–21] are the first choice for bleeding cases because these are the simplest and least invasive ways to treat duodenal varices (Fig. 37.5). Drugs used in endoscopic treatment included Histoacryl®, ethanolamine oleate (EO), and Aethoxysklerol (AS) in 12, 6, and 1 cases out of 19, respectively [1].

IVR treatments used to treat duodenal varices include percutaneous transhepatic obliteration (PTO) [22, 23], balloon-occluded retrograde transvenous obliteration (B-RTO) [24–27], trans-ileocolic venous obliteration [28], and dual balloon-occluded embolotherapy (DBOE) [29]. Furthermore, in cases where the efficacy of endoscopic treatment is temporary, a combination of endoscopic treatment and IVR treatment has been applied [28, 30, 31].

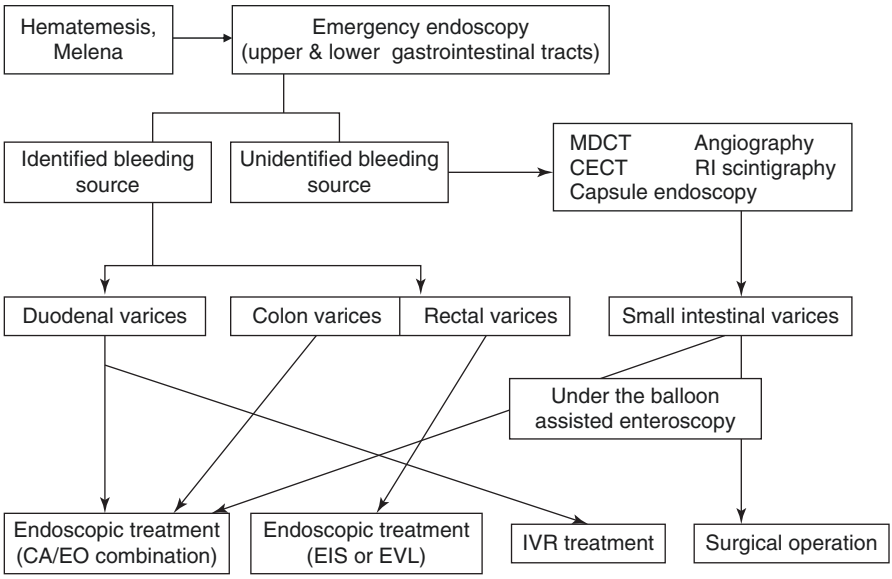


Fig. 37.4 Treatment strategies for ectopic varices. *MDCT* multidetector-row computed tomography, *CECT* contrast-enhanced computed tomography, *RI* radioisotope, *CA* cyanoacrylate, *EO* ethanolamine oleate, *EIS* endoscopic injection sclerotherapy, *EVL* endoscopic variceal ligation, *IVR* interventional radiology

Surgical operations such as partial resection of the duodenum accompanied by devascularization, variceal ligation, or portosystemic shunting have been carried out for a long time; however, in recent years, surgery has been applied as a salvage method in elective cases where endoscopic or IVR treatment is not applicable [32]. Furthermore, in cases where open abdominal surgery is contraindicated because of the patient's poor clinical condition, laparoscopic resection of duodenal varices can be an alternative treatment.

As the treatment of duodenal varices is controversial particularly in cases where the blood flow inside the varices is hepatopetal, at our institute, patients exhibiting this condition are followed periodically on an outpatient basis without treatment.

37.3.2 Colorectal Varices

In patients with portal hypertension, hepatofugal collaterals form as shunts that divert the blood flow from the increased intrahepatic vascular resistance. They tend to develop in association with colorectal varices in the inferior mesenteric veins, through which blood flows retrograde via the rectal venous plexus and into the general circulation. Apart from the esophagogastric region, the rectum is the region where portosystemic shunts are prone to develop most frequently.

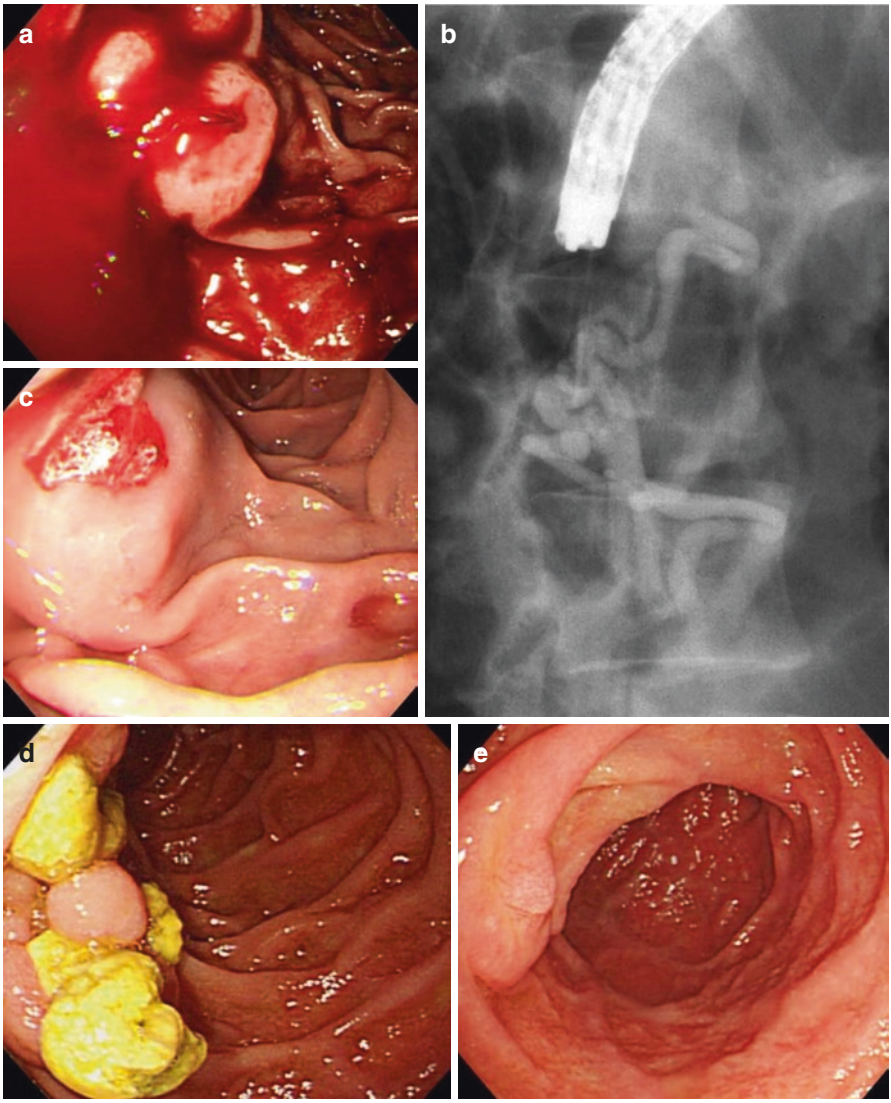


Fig. 37.5 Endoscopic treatment of bleeding duodenal varices. Male aged 25 with EHO and a history of receiving treatment for gastric varices. (**a**) Emergency endoscopy revealed spurting bleeding from varices located in the descending part of the duodenum. (**b**) Under fluoroscopy, 75% αCA was injected at a point adjacent to the bleeding point until the feeding veins, and parts of the drainage veins were visualized. (**c**) Just after αCA injection, endoscopic imaging revealed that the bleeding point was occluded with αCA polymer. (**d**) Five months after the treatment, endoscopic imaging showed the αCA polymer had recently been falling off. (**e**) Endoscopic imaging 3.5 years after treatment showed that the αCA polymer had completely fallen off with no recurrence of bleeding. *EHO* extrahepatic portal obstruction, *αCA* α-cyanoacrylate monomer

According to a questionnaire survey in 2010, underlying diseases of colorectal varices reportedly included liver cirrhosis in 63.9% of the cases followed by EHO in 11.1% and IPH in 11.1%, respectively [1], while in our data on 22 patients, 68.2% (15 out of 22 patients) had liver cirrhosis, 18.2% (4/22) had EHO, 9.1% (2/22) had IPH, and 4.5% (1/22) had a history of congenital biliary atresia [8].

The locations of colorectal varices were the rectum in 66.7%, the sigmoid colon in 22.2%, the intestinal cecum in 16.7%, and overall colorectal lesions in 2.8% of the cases [1], while our data showed that the rectal varices accounted for 90.9% (20/22) of all the colorectal varices and the varices found in overall colorectal lesions for 9.1% (2/22) [8] (Fig. 37.6).

37.3.2.1 Rectal Varices

Clinical Characteristics

There have been conflicting reports regarding the occurrence of rectal varices after the obliteration of esophageal varices. However, a large series of studies conducted in Japan showed that 95% of patients with rectal varices had a history of esophageal varices and 87% of these patients had previously undergone endoscopic variceal obliteration for esophageal varices [1]. The mechanism for generating rectal varices after the treatment of esophageal or gastric varices is thought to be caused by the obliteration of the supplying vessels such as the left gastric, posterior gastric, and short gastric veins, which leads to development of collateral vessels in the inferior mesenteric venous system, eventually resulting in the formation of rectal varices. Furthermore, the most frequent afferent vessel was the inferior mesenteric vein, followed by the superior rectal vein, and the efferent vessels included the internal iliac vein and the inferior rectal vein [1].

Rectal varices reportedly develop in 10–20% of patients with liver cirrhosis, and our data showed that rectal varices were found in 20 patients (1.7%) out of 1149 patients who received treatment of esophagogastric varices [8]. Sato et al. [7] reported 32 (2.6%) out of 1218 patients with portal hypertension had rectal varices, while Shudo et al. [12] reported that rectal varices were observed in 40 (9.4%) out of 425 patients with portal hypertension, among which bleeding occurred in 15 patients (37.5%).

Symptoms and Diagnosis

For bleeding cases, differentiation from hemorrhoids or anorectal varices and detection of the bleeding source are critical, for which colonoscopy is the first modality to be performed, whereas in cases of massive bleeding in which colonoscopy cannot

maintain a clear visual field, selective mesenteric arteriography or percutaneous transhepatic portography can provide useful findings for diagnostic evaluation in most cases. Diagnostic modalities for nonbleeding cases include barium enema examination, EUS, abdominal CT, and 3D-CT.

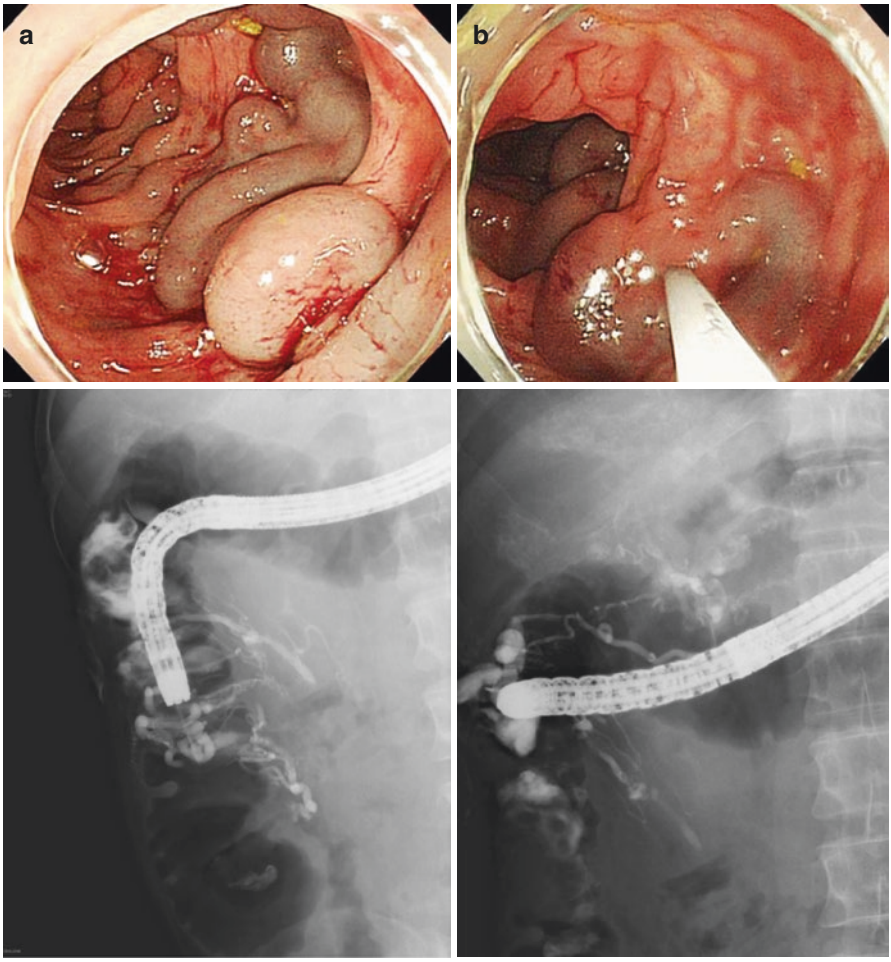


Fig. 37.6 Endoscopic treatment of colorectal varices. Female in her 40s with extrahepatic portal venous obstruction. Contrast enhanced X-ray imaging revealed a rapid blood flow in the ascending colon varices, and the varices were treated using 62.5% αCA (**a**) followed by obliteration of the feeding veins with EIS using 5% EO (αCA /EO combination method) (**b**). As blood flow in the sigmoid varices was slow, and contrast enhanced X-ray images were clearly obtained, the varices were treated using 5% EO (EO method) (**c**). Rectal varices were successfully treated using 5% EO (EO method) (**d**). *αCA* α-cyanoacrylate monomer, *EIS* endoscopic injection sclerotherapy, *EO* ethanolamine oleate

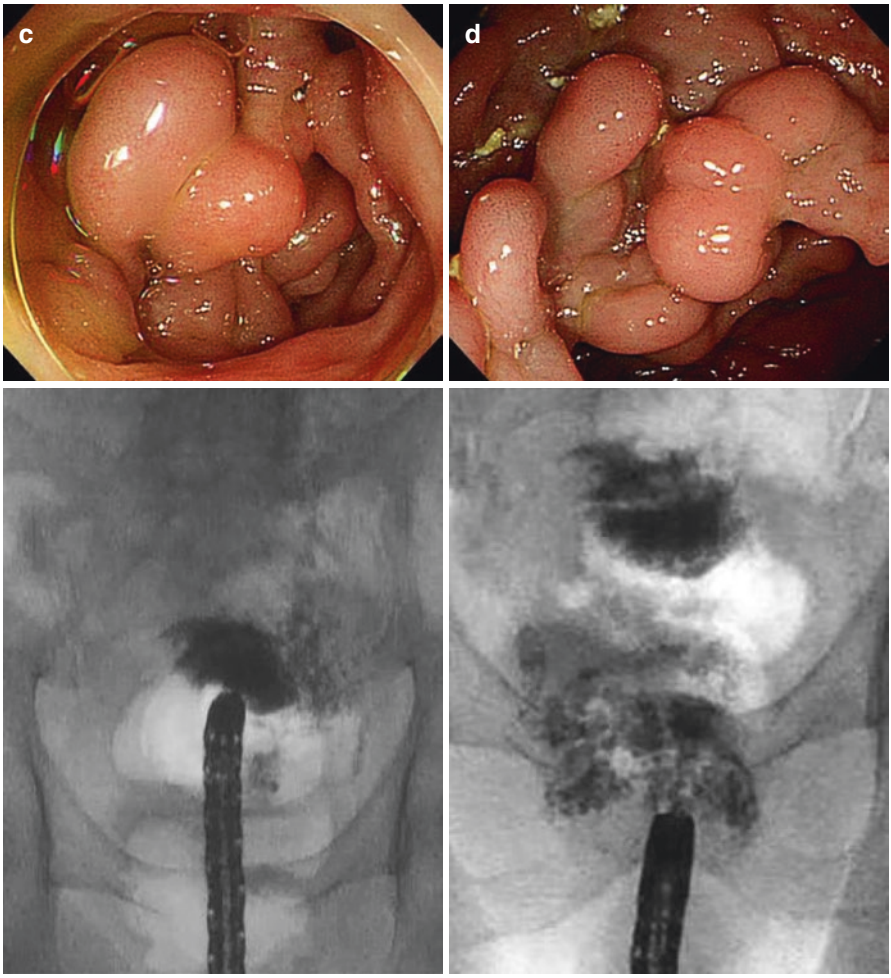


Fig. 37.6 (continued)

Treatment

No clear consensus has been reached on the established treatment method for rectal varices. Treatment should be performed taking into considerations patients' general conditions and portal hemodynamics. Of the feeding veins for rectal varices, the inferior mesenteric vein accounted for 29.8%, followed by superior rectal veins, which accounted for 12.3%. The drainage veins were the internal iliac vein and the inferior rectal veins, accounting for 15.8% and 14.0%, respectively [1].

For bleeding cases, endoscopic treatment was performed in 53.3% of the patients with rectal varices, followed by IVR in 13.3%, and combination of endoscopic treatment and IVR in 20%. If no qualified endoscopists or surgeons are readily available, apply balloon tamponade using a Sengstaken-Blakemore tube to stop the bleeding, and after hemostasis has been achieved, apply elective treatment while managing the patient's general condition. Furthermore, antihypertensive drugs such as vasopressin or propranolol can be used as additional treatments. Endoscopic treatment was applied in 53.3% of elective cases and in 85.7% of the prophylactic cases. Surgical operation was performed in 40% of the elective cases, while no surgical operation was applied in the prophylactic cases [1].

Treatment Techniques

The first case report of successful EIS was presented by Wang et al. for the treatment of bleeding rectal varices in 1985 [33]. Sato et al. [34] performed EIS using 5% ethanolamine oleate with iopamidol in 32 patients with rectal varices. After EIS, colonoscopy revealed shrinkage of the rectal varices in all 32 patients with no serious complications. The recurrence rate for rectal varices was 24.0% over a 1-year follow-up period with one bleeding recurrence. EVL has also been successfully performed for the treatment of rectal varices [35, 36]. However, a retrospective study comparing EIS and EVL in 34 patients [37] showed that recurrence rate was greater with EVL, and all four cases of bleeding recurrence during 1-year follow-up period were EVL cases. On the other hand, although EVL by itself is a safe treatment, the high prevalence of recurrence after EVL necessitates periodical follow-up endoscopy after treatment.

IVR treatments, such as PTO [38] and DBOE [39], and surgical operations such as shunting [40], rectal transection [41], and surgical suture [36] have also been performed.

37.4 Treatment Outcomes

In a 2010 national survey in Japan, out of 113 cases of treated ectopic varices, complete eradication was achieved in 62 cases (54.9%), while remaining varices and recurrence were found in 40 cases (35.4%) and 11 cases (9.7%), respectively [1]. The rate of complete eradication observed for rectal varices was 40.8%, which was significantly lower than the 73.4% observed for duodenal varices. At the end of the 5-year survey, 89 (57.1%) of the total population of 156 patients were confirmed to be still alive, while 50 patients (32.1%) were confirmed as deceased. No significant differences were observed in the prognosis after treatment according to the location of the ectopic varices [1]. Sato et al. [7] reported in 2011 that 43 patients with ectopic varices out of 1218 patients with portal hypertension were successfully treated. The number of cases, locations of ectopic varices, and used techniques were as follows: (1) 32 rectal varices, EIS or EVL;

(2) 3 duodenal varices, 2 B-RTO and 1 PTO; (3) 3 vesical varices, PTO; (4) 3 colonic varices, 2 PTO and 1 EIS; and (5) 1 stomal varix, transjugular intrahepatic portosystemic shunt.

37.5 Conclusion

Up to the present, no consensus has been reached on the management of ectopic varices. It is important to fully study the general condition, hepatic reserve, and portal hemodynamics of individual patients before providing them with an optimal treatment. Moreover, as data on ectopic varices continues to accumulate, an evidence-based consensus regarding the management of ectopic varices should be discussed based on this data. Lastly, a large case series of studies is necessary before evidence-based treatment recommendations can be made.

References

1. Watanabe N, Toyonaga A, Kojima S, Takashimizu S, Oho K, Kokubu S, Nakamura K, et al. Current status of ectopic varices in Japan: results of a survey by the Japan Society for Portal Hypertension. Hepatol Res. 2010;40:763–76.
2. Alberti W. Uber den Rontgenologischen Nachweis von Varizen im Bulbus duodeni. Fortschr Gep Rontgenstr. 1931;43:60–5.
3. Nishioka K, Kanetake Y, Matsui E, Imaeda T. Suspected case of varicose veins of the duodenum. Rinsho Hoshasen. 1968;13:305–12. [In Japanese].
4. Cabot RC, Castleman B, Towne VW. Case 40102. N Engl J Med. 1954;250:434–8. https://doi.org/10.1056/NEJM195403112501008.
5. Kumagai Y, Omori Y, Takeda Y, Makuuchi H. Rare gastrointestinal varices. In: Makuuchi Y, Yoshida M, editors. EIS for esophagogastric varices. Tokyo: Bunkodo; 1992. p. 311–6. [In Japanese].
6. Kumagai Y, Makuuchi H, Omori Y. Rare gastrointestinal varices. In: Idezuki Y, editor. Supervised. Tokyo: Tokyo Igakusha;1995. p. 9–133. [In Japanese].
7. Sato T, Akaike J, Toyota J, Karino Y, Ohmura T. Clinicopathological features and treatment of ectopic varices with portal hypertension. Int J Hepatol. 2011;2011:960720. https://doi.org/10.4061/2011/960720.
8. Obara K. Treatment for ectopic varices. Endosc Dig. 2013;25:1411–6. [In Japanese].
9. Obara K. Gastroenterological varices: management of ectopic varices. Clin Gastroenterol. 2003;6:507–15. [In Japanese].
10. Portosystemic collaterals in location other than esophagogastric region. In: Takase Y. Supervised. Portosystemic vascular atlas for the treatment of varices. Tokyo: Igaku-Shoin Ltd;1999. p. 27. [In Japasnese].
11. Matsui S, Kudo M, Ichikawa T, Okada M, MIyabe Y. The clinical characteristics, endoscopic treatment, and prognosis for patients presenting with duodenal varices. Hepato-Gastroenterology. 2008;55:959–62.
12. Shudo R, Yazaki Y, Sakurai S, et al. Clinical study comparing bleeding and nonbleeding rectal varices. Endoscopy. 2002;34:189–94.
13. Barbish AW, Ehrinpreis M. Successful endoscopic injection sclerotherapy of a bleeding duodenal varix. Am J Gastroenterol. 1993;88:90–2.

14. Sato H, Fujishiro H, Rumi MA, Kinoshita Y, NIigaki M, Kohge N, et al. Successful endoscopic injection sclerotherapy for duodenal varices. J Gastroenterol. 2002;37:143–4.
15. Seo YS, Kwon YD, Prk S, Keum B, Prk BJ, Kim YS, et al. Complete eradication of duodenal varices after endoscopic injection sclerotherapy with ethanolamine oleate: a case report. Gastrointest Endosc. 2008;67:759–62.
16. Shirai M, Hiroyasu S, HIga T, Oshiro S, Muto Y. Successful management of ruptured duodenal varices by means of endoscopic variceal ligation: report of a case. Gastrointest Endosc. 1999;49:255–7.
17. Tazawa J, Saki Y, Koizumi K, et al. Endoscopic ligation for ruptured duodenal varices. Am J Gastroenterol. 1995;9:677–8.
18. Kawakami Y, Takahashi H, Kato S, Uchiyama T, Mawatari H, Iida H, et al. Effective treatment for duodenal variceal bleeding using endoscopic ligation. Hepato-Gastroenterology. 2011;58:2024–5.
19. Suzuki R, Irisawa A, HIkichi T, Shibukawa G, Takagi T, Wakatsuki T, et al. Hemorrhagic duodenal varices treated successfully with endoscopic injection sclerotherapy using cyanoacrylate and ethanolamine-oleate: a case report. Surg Laparosc Endosc Percutan Tech. 2009;19:e233–6. www.surgical-laparoscopy.com/e233.
20. Ota K, Shirai Z, Matsuzaki T, Tanaka K, Higashihara H, Okazaki M, et al. Endoscopic injection sclerotherapy with N-butyl-2-cyanoacrylate for ruptured duodenal varices. J Gastroenterol. 1998;33:550–5.
21. Yoshida Y, Imai Y, Nishikawa M, Kurokawa M, Shibata K, et al. Successful endoscopic injection sclerotherapy with N-butyl-2-cyanoacrylate following the recurrence of bleeding soon after endoscopic ligation for ruptured duodenal varices. Am J Gastroenterol. 1997;92:1227–9.
22. Chikamori F, Shibuya S, Takase Y. Percutaneous transhepatic obliteration for esophagojejunal varices after total gastrectomy. Abdom Imaging. 1998;23:560–2.
23. Sato T, Yamazaki K, Toyota J, Karino Y, Ohmura T, Akaike J, et al. Efficacy of color Doppler ultrasonography for the diagnosis of duodenal varices successfully treated with percutaneous transhepatic obliteration. J Med Ultrason. 2007;34:59–63.
24. Sonomura T, Horihata K, Yamahara K, Dozaiku T, Toyonaga T, Hiroka T, et al. Ruptured duodenal varices successfully treated with balloon-occluded retrograde transvenous obliteration: usefulness of microcatheters. AJR Am J Roentgenol. 2003;181:725–7.
25. Ohta M, Yasumori K, Saku M, et al. Successful treatment of bleeding duodenal varices by balloon-occluded retrograde transvenous obliteration: a transjugular venous approach. Surgery. 1999;126:581–3.
26. Hotta M, Yoshida H, Mamada Y, Taniai N, Bando K, Mizuguchi Y, et al. Succeessful management of duodenal varices by balloon-occluded retrograde transvenous obliteration. J Nippon Med Sch. 2008;75:36–40.
27. Hashimoto R, Sofue K, Takeuchi Y, Shibamoto K, Arai Y. Successful balloon-occluded retrograde transvenous obliteration for bleeding duodenal varices using cyanoacrylate. World J Gastroenterol. 2013;19:951–4.
28. Ohta K, Okazaki M, Higashihara H, Kokawa H, Shirai Z, Anan A, et al. Combination of transileocolic vein obliteration is effective for ruptured duodenal varices. J Gastroenterol. 1999;34:694–9.
29. Takamura K, Miyake H, Mori H, Terashima Y, Ando T, Fuji M, et al. Balloon occluded retrograde transvenous obliteration and percutaneous transhepatic obliteration for ruptured duodenal varices after operation for rectal cancer with multiple liver metastasis: report of a case. J Med Invest. 2005;53:212–7.
30. Haruta I, Isobe Y, Ueno E, et al. Balloon-occluded retrograde transvenous obliteration(BRTO), a promising nonsurgical therapy for ectopic varices: a case report of successful treatment of duodenal varices by BRTO. Am J Gastroenterol. 1996;91:2594–7.
31. Akazawa Y, Murata I, Yamao T, Yamakawa M, Kawano Y, Nomura N, et al. Successful management of bleeding duodenal varices by endoscopic variceal ligation and balloon-occluded retrograde transvenous obliteration. Gastrointest Endosc. 2003;58:794–7.

32. Wang CS, Jeng LB, Chen MF. Duodenal variceal bleeding: successfully treated by mesocaval shunt after failure of sclerotherapy. Hepato-Gastroenterology. 1995;42:59–61.
33. Wang M, Desigan G, Dunn D. Endoscopic sclerotherapy for bleeding rectal varices: a case report. Am J Gastroenterol. 1985;80:779–80.
34. Sato T. Efficacy of endoscopic injection sclerotherapy for rectal varices. J Gastroenterol Hepatol Res. 2013;2:359–61.
35. Sato T. Two cases of rectal varices treated by endoscopic variceal ligation. Dig Endosc. 1999;11:66–9.
36. Yoshino K, Imai Y, Nakazawa M, Chikayama T, Ando S, Sugawara K, et al. Therapeutic strategy for patients with bleeding rectal varices complicating liver cirrhosis. Heparol Res. 2014;44:1088–94.
37. Sato T, Yamazaki K, Akaike J, Toyota J, Karino Y, Ohmura T. Retrospective analysis of endoscopic injection sclerotherapy for rectal varices compared with band ligation. Clin Exp Gastroenterol. 2001;3:159–63.
38. Okazaki H, Higuchi K, Shiba M, Nakamura S, Wada T, Yamamori K, et al. Successful treatment of giant rectal varices by modified percutaneous transhepatic obliteration with sclerosant: report of a case. World J Gastroenterol. 2006;12:5408–11.
39. Kimura T, Haruta I, Isobe Y, Ueno E, Toda J, Nemoto Y, et al. A novel therapeutic approach for rectal varices: a case report of rectal varices treated with double balloon-occluded embolotherapy. Am J Gastroterol. 1997;92:883–6.
40. Sato Y, Yokoyama N, Suzuki S, Tani T, Nomoto M, Hatakeyama K. Double selective shunting for esophagogastric and rectal varices in portal hypertension due to congenital hepatic polycystic disease. Hepato-Gastroenterology. 2002;49:1528–30.
41. Katakura K, Irisawa A, Obara K, Saito A, Shishido H, Shibukawa G, et al. Appearance of rectal varices in extrahepatic portal obstruction after treatment for esophago-gastric varices: a case report. Fukushima J Med Sci. 2002;48:51–6.

Chapter 38
Interventional Radiology: Balloon-Occluded Retrograde Transvenous Obliteration

Shozo Hirota, Kaoru Kobayashi, and Koichiro Yamakado

Abstract Balloon-occluded retrograde transvenous obliteration (B-RTO) is a transcatheter treatment for gastric varices that are difficult to treat by endoscopic injection sclerotherapy. A balloon catheter is wedged into the main drainage vein of the gastric varices, such as gastrorenal shunt, and sclerosing agent (ethanolamine oleate with contrast media) is retrogradely injected into the gastric varices under balloon occlusion of the drainage vein. More than 5 hours of bed rest is recommended until the hard thrombus is formed in the varices. Many collateral veins appear after balloon occlusion, and understanding of the hemodynamics of the portal system is important. The success rate of thrombosis of gastric varices is high and the rebleeding rate is low. After B-RTO hepatic function reserve improved in about half of the patients due to restoration of the hepatopetal portal flow. Recently plug-assisted retrograde transvenous obliteration (PARTO) has been developed, in which a vascular plug is used instead of a balloon catheter.

Keywords Gastric varices · Gastrorenal shunt · Hepatic encephalopathy · Ethanolamine oleate · Vascular plug

38.1 Introduction

The number of patients with viral hepatitis and liver cirrhosis exceeds three million in the United States, and how to deal with esophageal varices and gastric varices caused by portal hypertension (PH) accompanying viral hepatitis and liver cirrhosis has become an important issue [1].

There are four therapeutic procedures for PH: endoscopic treatment, surgery, interventional radiology, and conservative treatment. Because of the broad range of

S. Hirota (✉)
IVR Center, Konan Hospital, Hyogo, Japan

K. Kobayashi · K. Yamakado
Department of Radiology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_38

therapeutic coverage, interventional radiology has in recent years become important in the treatment of portal hypertension. Interventional radiology started with percutaneous transhepatic obliteration (PTO) [2, 3] and partial splenic embolization (PSE) [4], and the efficacy has been widely recognized since Rosch developed the transjugular intrahepatic portosystemic shunt (TIPS) [5]. In Japan, on the other hand, balloon-occluded retrograde transvenous obliteration (B-RTO) [6–12] was developed in 1996 as a transcatheter treatment for gastric varices that were difficult to treat by endoscopic injection sclerotherapy, and the beneficial therapeutic effect has been proven over the last 10 years. In this chapter, we describe the treatment rationale, therapeutic technique, and results of B-RTO.

38.2 Hemodynamics of Gastric Varices and B-RTO

The supply routes for gastroesophageal varices are the left gastric vein and short/posterior gastric vein. The former is the major route for esophageal varices, and the latter is the major route for gastric varices. The blood that pours into the gastric varices on the posterior wall of the gastric fornix descends to flow from the inferior phrenic vein into the renal vein via the adrenal vein. This is called the gastrorenal shunt (GR shunt). In the ascending route, on the other hand, the blood joins the flow in the pericardial vein to pour into the inferior vena cava just above the left hepatic vein (Fig. 38.1).

Because a large volume of blood flows quickly in gastric varices, mortality due to rupture is high. They are located in the fornix, a site where hemostasis procedure is difficult, so it is not easy to perform endoscopic treatment.

With B-RTO, a balloon catheter is placed retrogradely in the GR shunt or the inferior phrenic vein flowing into the inferior vena cava so that sclerosant can be injected into the gastric varices for thrombus formation while the blood flow is cut off.

38.3 Indications

38.3.1 Indication

1. Emergency cases of gastric varices with rupture and cases of gastric varices with a history of rupture or in danger of rupture that have a GR shunt
2. Cases with hepatic encephalopathy due to a GR shunt

38.3.2 Relative Indications

1. Hepatic encephalopathy due to portosystemic shunt – attributable to mesocaval shunt, etc.
2. Bleeding: venous shunt attributable to portal hypertension such as duodenal varices and mesenteric varices

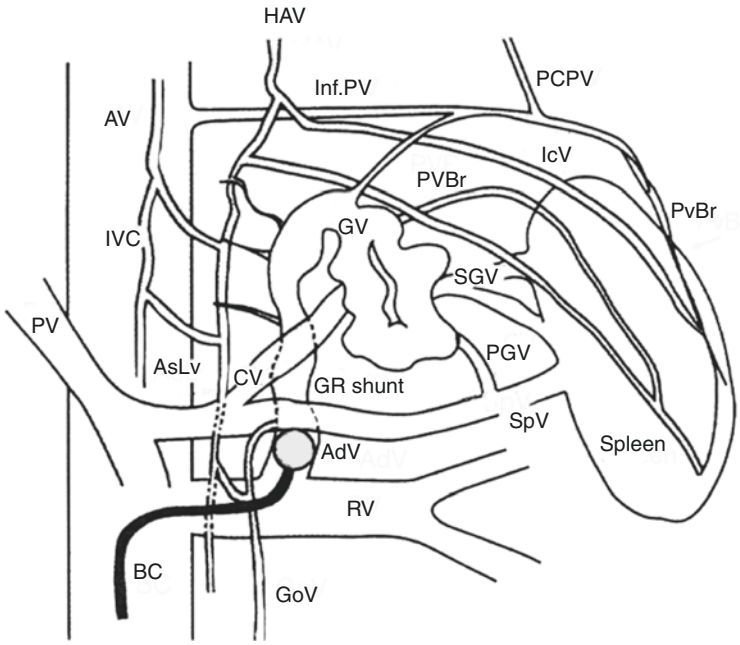


Fig. 38.1 Hemodynamics of the gastric fundal varices and collateral veins. *AdV* adrenal vein, *AsLV* ascending lumbar vein, *AV* azygos vein, *BC* balloon catheter, *CV* coronary vein or left gastric vein, *IPV* inferior phrenic vein, *IVC* inferior vena cava, *GoV* gonadal vein, *GR shunt* gastrorenal shunt, *GV* gastric varices, *HAV* hemiazygos vein, *IcV* intercostal vein, *PCPV* pericardiacophrenic vein, *PGV* posterior gastric vein, *PV* portal vein, *PvBr* branch of inferior phrenic vein, *RV* renal vein, *SGV* short gastric vein, *SpV* splenic vein

38.3.3 Relative Contraindication

Cases in which contrast agent flows easily from the shunt into the portal vein. B-RTO is not indicated for these cases because the sclerosant, i.e., an embolizing agent, may drain.

38.4 Preoperative Procedures

38.4.1 Checking the GR Shunt

The GR shunt should be thoroughly examined by CT (Fig. 38.2). The left inferior phrenic vein may be seen on the CT scan. The hemodynamics should be clearly studied.

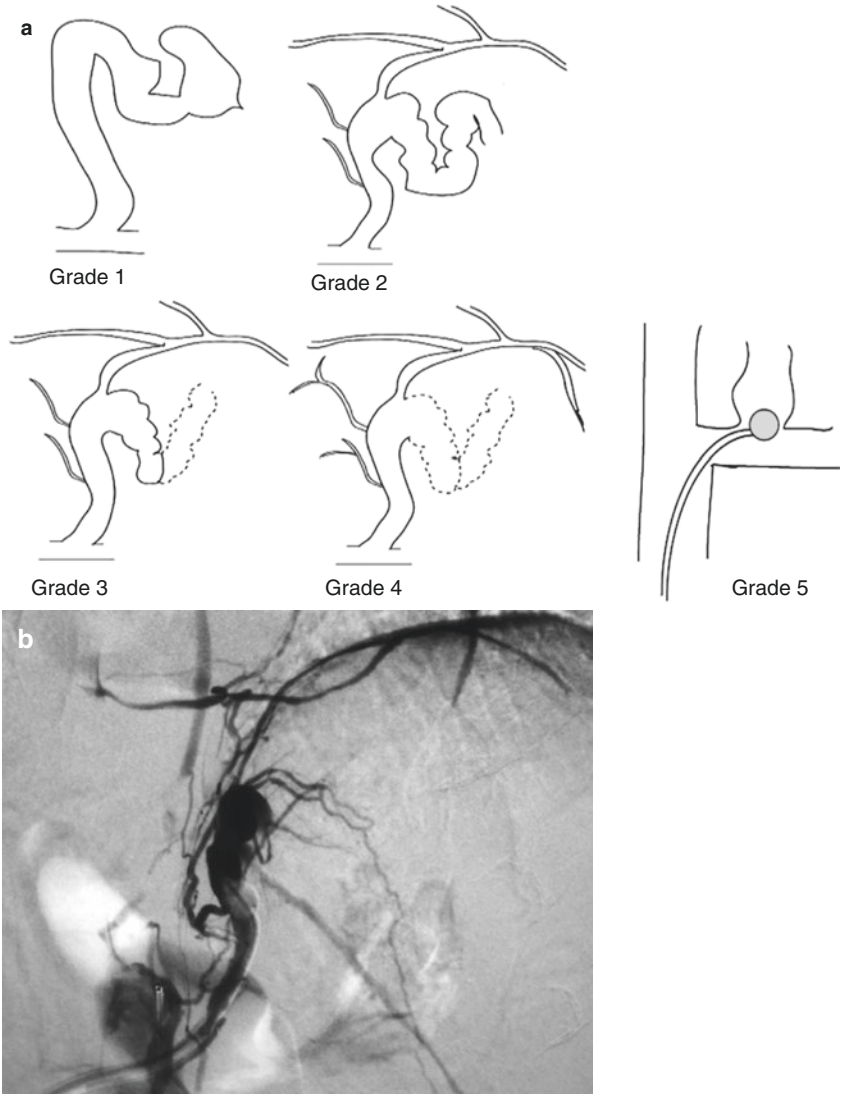


Fig. 38.2 (**a**) Diagrams of the grades of progression of gastric varices and collateral veins: grade 1, gastric varices were well-opacified without evidence of collateral veins; grade 2, collateral veins were small and a few in number, and the contrast medium remained in the gastric varices for 3 min or more; grade 3, collateral veins were medium to large, there were a few veins, and the contrast medium filled the gastric varices only partially and disappeared within 3 min; grade 4, there were many large collateral veins, and the gastric varices are not opacified. (**b**) Balloon-occluded retrograde transvenous venography shows many collateral veins and a part of the gastric varices. This case was diagnosed as grade 3 collateral vein development

38.4.2 Classifying the Gastric Varices According to Endoscopic Findings

There are three types of gastric varices when classified according to endoscopic findings: Lg-c, Lg-cf, and Lg-f. Lg-c refers to the gastric varices located at the cardiac ring, and Lg-f refers to isolated gastric varices found in the fornix, apart from the cardiac ring. Lg-cf refers to gastric varices that continue from the cardiac ring to the gastric fornix. Hemodynamically, the short gastric vein and posterior gastric vein are the supply routes for Lg-f and flow into the GR shunt. B-RTO is most suitable for the Lg-f type but is also performed on the Lg-cf type.

38.4.3 Preparation of Drugs

38.4.3.1 Preparation of 5% EOI (Ethanolamine Oleate with Iodinated Contrast Media)

One vial of EO (ethanolamine oleate, Oldamin [Takeda Chemical Industries, Ltd.]; 10 mg/vial) is dissolved in 10 mL of nonionic contrast medium to prepare the 5% EOI. EO is a sclerosant used for varices [13]. The maximum single dose of 5% EOI is 20 mL.

38.4.3.2 Absolute Ethanol

Absolute ethanol is used concomitantly to occlude the small collateral veins or when the amount of EOI exceeding the maximum single dose is used for large varices.

38.4.3.3 Foam Sclerosant

Foam sclerosant is used in the United States and in Japan. Three percent sodium tetradecyl sulfate (STS) or 3% polidocanol is mixed with contrast media and air. Matsumoto et al. [14] reported the rate of mixture; Lipiodol/STS/air = 1:2:3.

38.4.3.4 Haptoglobin

To prevent renal failure due to hemolysis attributable to the red cell membrane destroyed by EOI, haptoglobin 4000 units (Mitsubishi Pharma Corporation, Japan) is intravenously injected both preoperatively and perioperatively [15]. Haptoglobin is a therapeutic agent for hemoglobinemia and hemoglobinuria due to hemolytic reaction, and 1 unit combines with 1 mg hemoglobin.

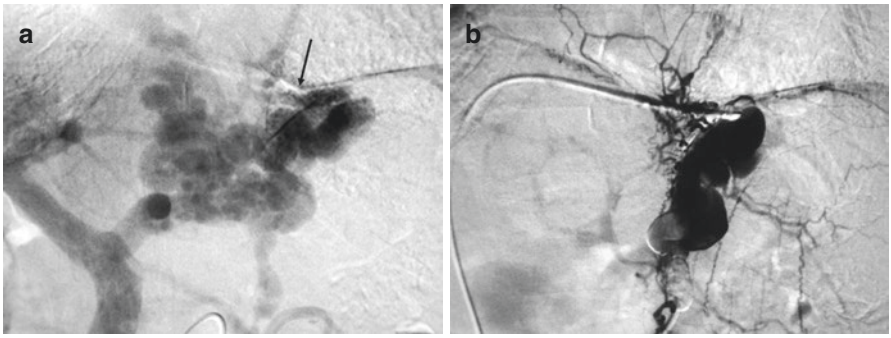


Fig. 38.3 A 70-year-old man with grade 3 gastric varices. (**a**) SMA portography shows huge gastric varices which left gastric vein feeds mainly and shows two drainage veins, inferior phrenic vein (*arrow*) and gastrorenal shunt. (**b**) After gastrorenal shunt and left inferior phrenic vein were occluded with balloon inflation, respectively, venography was taken. Then sclerosant, 5% EOI, was injected

38.4.4 Preparation of the Catheter

1. A 6-F occlusion balloon catheter (Clinical Supply Co., Gifu, Japan) with a balloon diameter of 20 mm and balloon length of 20 mm is frequently used. A balloon diameter of 10 mm or over is required (Fig. 38.3).
2. An 8-F guiding sheath (Medikit Co., Tokyo Japan).
3. Microcatheter (2.1-F) (Sniper 2, Terumo, Tokyo) or a 2.7-F microcatheter (Progreat; Terumo, Tokyo, Japan).

38.5 Procedure

38.5.1 Superior Mesenteric Angiography and Celiac Angiography

Angiography is performed to reaffirm the hemodynamics. Prostaglandin is used for portography in superior mesenteric angiography. Angiography is performed via the left femoral artery because the right groin is used for the venous route.

38.5.2 Catheter Insertion into the GR Shunt

There are two approaches: the transfemoral venous approach and transjugular venous approach. An 8-F guiding sheath is inserted from the right femoral vein into the GR shunt. A commonly used multipurpose 6-F balloon catheter with a slight angle is inserted into the GR shunt to perform angiography under balloon occlusion. A wedge catheter facilitates the procedure and requires less EOI (downgrading technique) [10] (Fig. 38.4).

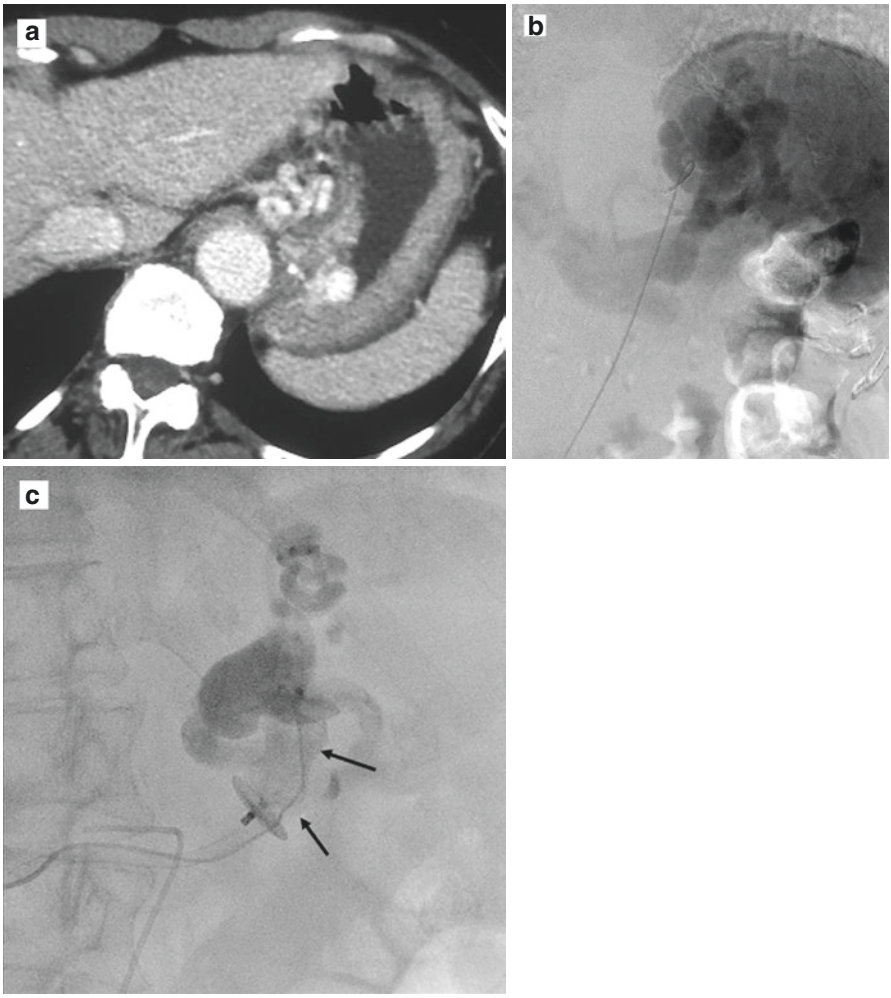


Fig. 38.4 PARTO case. 73-year-old woman with gastric varices and hyperammonemia. (**a**) On contrast enhanced CT, a large gastric varix was recognized. (**b**) On the venous phase of celiac arteriography, a huge gastric varix received blood flow from the left gastric vein and drained into the gastrorenal shunt. (**c**) A vascular plug (type 2, 22 mm in diameter) (*arrow*) was placed to the GR shunt. Sclerosing agent was injected via another 2.3-F microcatheter placed beforehand. Modified PARTO was successfully finished

38.5.3 Checking the Development of Collateral Veins

Angiography under balloon occlusion of the GR shunt reveals many collateral veins (Fig. 38.1). The inferior phrenic veins are the largest in number, and the pericardial vein is frequently dilated in the angiographic images. The ascending lumbar vein and small veins of the accessory hemiazygos vein system often become the

collateral veins. Sclerosant injected under these circumstances does not flow into the gastric varices but drains into the inferior vena cava and the azygos venous system from the collateral veins. Therefore, it is necessary to occlude the collateral veins carefully. We grade the collateral veins and occlude the collateral veins accordingly (see Fig. 38.2 for grading of the collateral veins) [7]. The grade 1 and 2 collateral veins rarely need occlusion, but grade 3 and higher veins require occlusion. For grade 4 or 5, concomitant use of a balloon catheter that is inserted into the left gastric vein under percutaneous transhepatic portography (PTP) to stop the blood flow can be adopted.

Contrast X-ray examination of the shunt is performed under balloon occlusion to grade the development of collateral veins and the gastric varices [7].

Grade 1: Only the gastric varices are opacified.
Grade 2: The entire body of the gastric varices as well as the inferior phrenic veins and some small veins is depicted. The contrast medium does not wash out immediately.
Grade 3: More collateral veins are seen than in grade 2, and the gastric varices are only partially depicted.
Grade 4: Only the collateral veins are depicted, and the gastric varices are not opacified.
Grade 5: The GR shunt shows dilation exceeding 30 mm, and the balloon catheter is swept away by the flow of blood into the renal vein.

38.5.4 Occlusion of the Collateral Veins and 5% EOI Injection into the Varices

38.5.4.1 Technique of the Catheter Advancement

For grade 1, the collateral veins can be occluded by EOI alone. As the grade progresses from 2 to 4, however, small amount of ethanol, metal coil, etc. are required. For grade 2 to 4, the downgrading technique [10] is performed once, and if this is successful, no occlusion of the collateral veins is required. For downgrading, a 2.7-F microcatheter (Progreat; Terumo, Tokyo, Japan) is advanced with use of the attached microwire through the previously introduced balloon catheter, managing to pass by as many collateral vessels as possible and finding a position close to the main variceal body. This microcatheter with attached microwire is then used to attempt selective catheterization of the varices. Next, a 6-F balloon catheter is carefully advanced over the microcatheter through the gastrorenal shunt just distal to the varices. Sometimes, we use a 0.035 hydrophilic guidewire (Radifocus; Terumo, Tokyo, Japan) before using a 2.7-F microcatheter. Fukuda et al. reported that 13 of 15 patients (86.6%) with more than grade 3 had their gastric varices successfully downgraded [10].

38.5.4.2 Technique in Cases of Grade 4 or 5

When a catheter cannot be inserted from the inferior vena cava into the inferior phrenic vein in grade 4, some of the many collateral veins are occluded with ethanol or coil as much as possible by using a microcatheter. The balloon is then inflated in the GR shunt to inject a small amount of absolute ethanol and approximately 20 mL of 5% EOI. The EOI drains into the remaining small collateral veins in a short period, but the number of collateral veins is markedly decreased, and the B-RTO procedure is easily performed when B-RTO is performed again 1 or 2 weeks later. In some cases of grade 5, percutaneous transhepatic insertion of a balloon catheter into the left gastric vein is needed due to the high flow of blood, while inserting another balloon catheter into the left adrenal vein by the usual method to perform B-RTO by obstructing both veins.

38.5.5 Injection of 5% EOI into the Varices

EOI injection can be reliably performed without excessive venous occlusion if a microcatheter is superselectively inserted from inside the balloon catheter into the gastric varices to inject or fill EOI. We have set the maximum injection volume of EOI at 30 mL [7]. The gastric varices are opacified by the imaging ability of EOI. Embolization of varices can be fully expected if EOI is not injected until the left gastric vein is depicted.

38.5.5.1 Balloon Inflation Time

After EOI injection, the catheter is placed for 5 hours or longer under balloon occlusion. When B-RTO is started in the afternoon and completed in the evening, the patient returns to his/her room, and the catheter remains in place until the following morning. Angiography is performed for confirmation the following morning in the angiography room, and the balloon is deflated and removed. If the balloon occlusion time is short, the thrombus in the gastric varices or the GR shunt may move to cause severe pulmonary embolization.

Some medical facilities including us leave the catheter in place until the following morning.

38.6 Clinical Results

The items summarized below were analyzed in 145 patients who underwent B-RTO [12].

38.6.1 Technical Success Rate

The success rate of B-RTO at our institute was 93%. (Success was defined as the disappearance or marked reduction of the varices after single or repeated B-RTO procedures.) Other studies reported 95–100% success rates [6–8], but they were based on smaller data sets than in our study.

38.6.2 Hepatic Encephalopathy

Thirteen out of 14 patients (93%) showed an improvement in encephalopathy. Shunt-related hepatic encephalopathy due to the increased shunt blood flow can be dramatically improved by closing the shunt via B-RTO if the GR shunt is the primary shunt [6, 7]. In many cases, however, many other shunts exist, and mild hepatic encephalopathy may remain when only the GR shunt is closed. In these cases, it is necessary to consider closing the other shunts.

38.6.3 Aggravation of Esophageal Varices

Approximately 25–40% of esophageal varices are aggravated after B-RTO, for which endoscopic treatment may be required [8]. In the Lg-cf type, the esophageal varices are thought to be worse in the route from the left gastric vein to the esophageal vein.

38.6.4 Changes in Liver Function

The increased portal blood flow improves the hepatic reserve. In this study, 48% (44/91 patients) showed an improvement in liver function. Clinical improvement in liver function was defined as a decrease in the Child-Pugh score. B-RTO occludes the shunt by which the portal pressure is increased. In the meantime, the diverted blood flows toward the liver, and the increased hepatopetal flow improves the hepatic reserve. This is thought to induce the improvement in liver function. Because the hepatic volume is increased after B-RTO, B-RTO is expected to be a therapeutic measure for liver cirrhosis.

38.6.5 Liver Cancer

Liver cancer, which is known to be a prognostic factor [8], was seen in 42 cases.

38.7 Complications

Hematuria frequently appears, but it rarely leads to renal failure when haptoglobin is concomitantly used.

38.7.1 Pulmonary Edema and Hemothorax

Pulmonary edema and shock due to the use of EOI have been infrequently reported [16].

Some facilities set the maximum dose of EOI at 0.4 mL/kg. EO should be used carefully because pulmonary edema [17], hemothorax [18], DIC [19], and cardiogenic shock are caused by EO in rare cases. The volume of EOI can be reduced if it is injected after injection of 50% dextrose in water (D50W).

38.7.2 Allergic Reactions to Ethanol

There are some acute allergic reactions: (1) itchy mouth, eyes, or nose, (2) itchiness on the skin, (3) swelling of the face, (4) nasal congestion, (5) abdominal pain, and (6) dizziness. Physicians should take care of these symptoms and appropriate response should be taken.

38.7.3 Pain

Pain immediately after ethanol injection. Although ethanol (ethyl alcohol) can be a strong embolic material in the vessels, rapid injection causes acute alcohol poisoning. Bolus injection of approximately 15 g of absolute ethanol raises the blood alcohol level to 300–400 mg/100 mL, and there is a risk of coma. Care should be exercised to avoid excessive administration exceeding 15 g, and the patient's condition immediately after administration must be carefully observed.

38.7.4 Coil Migration

Coil migration has been infrequently reported to occur with the change in the direction of blood flow during coil embolization of the inferior phrenic vein. It is essential to use a considerably large coil.

38.7.5 Portal Thrombosis

Portal thrombosis can be caused by inflow of the sclerosant from the left gastric vein into the portal vein or from the splenorenal shunt into the splenic vein. In some cases, a splenorenal shunt joins the adrenal vein separately from the GR shunt. There is a possibility that EOI from the balloon catheter may flow into the splenic vein to produce thrombus in the portal vein. The blood flow should be checked thoroughly and carefully.

38.8 Plug-Assisted Retrograde Transvenous Obliteration (PARTO)

Gwon et al. [19] recently introduced the vascular plug-assisted retrograde transvenous obliteration (PARTO) as an alternative procedure that treats gastric varices. In PARTO, vascular plug and Gelfoam slurry were used to embolize gastric varices as well as collateral veins instead of sclerosing agent (Fig. 38.4). The advantage of PARTO is that there is no need of bed rest for more than 2 hours because all catheters are drawn after the procedure. Disadvantage is higher recurrence rate (32.8% in 1 year, 55.2% in 2 years) compared with B-RTO (3.2%, 16.5%) or B-RTO using Sotradecol (0%, 0%) [20]. Collateral embolization with Gelfoam slurry may be incomplete to occlude veins, and the main cause may be a fate of natural absorption of gelatin sponge. And in case of recurrence after PARTO, it is difficult to perform B-RTO again because of complete occlusion of the GR shunt.

38.9 Conclusions and Future Prospects

B-RTO is used to embolize the varices from downstream, in contrast to PTO, which embolizes the varices from upstream. B-RTO can be employed not only for gastric varices but also for duodenal varices [21, 22]. In many cases, the portal blood flow becomes hepatopetal again, and half of the patients that underwent B-RTO showed a secondary effect of improvement in liver function, revealing that B-RTO has a therapeutic effect on liver cirrhosis. Further development of B-RTO is fully expected.

References

1. Grant WC, Jhaveri RR, McHutchinson JG, Schulman KA, Kauf TL. Trends in health care resources use for hepatitis C virus infection in the United States. Hepatology. 2005;42:1406–13.
2. Lunderquist A, Borjesson B, Owman T, Bengmark S. Isobutyl-2-cyanoacrylate(bucrylate) in obliteration of gastric coronary vein and esophageal varices. AJR. 1978;130:1–6.

3. Nakao N, Sugiki K, Chin K, Miura K, Kyo A, Okamato E, Ishikawa Y, Uchida H. Transhepatic embolization of gastroesophageal varices in liver cirrhosis. Nippon Igaku Hoshasen Gakkai Zasshi. 1978;38:852–61.
4. Spigos DG, Tan WS, Mozes MF, Capek V. Partial splenic embolization in the treatment of hypersplenism. AJR. 1979;132:777–82.
5. Rosch J, Hanafee WN, Snow H. Transjugular portal venography and radiologic portocaval shunt; an experimental study. Radiology. 1969;92:1112–4.
6. Kanagawa H, Mima S, Kouyama H, et al. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. J Gastroenterol Hepatol. 1996;11:51–8.
7. Hirota S, Matsumoto S, Tomita M, et al. Retrograde transvenous obliteration of gastric varices. Radiology. 1999;211:349–56.
8. Fukuda T, Hirota S, Sugimura K. Long-term results of balloon-occluded retrograde transvenous obliteration for the treatment of gastric varices and hepatic encephalopathy. J Vasc Interv Radiol. 2001;12:327–36.
9. Hirota S, Ichikawa S, Matsumoto S, et al. Interventional radiologic treatment for idiopathic portal hypertension. Cardiovasc Intervent Radiol. 1999;22:311–4.
10. Fukuda T, Hirota S, Sugimoto K, Matsumoto S, Zamora CA, Sugimura K. "Downgrading" of gastric varices with multiple collateral veins in balloon-occluded retrograde transvenous obliteration. J Vasc Interv Radiol. 2005;16(10):1379–83.
11. Fukuda T, Hirota S, Matsumoto S, Sugimoto K, Fujii M, Tsurusaki M, Izaki K, Sugimura K. Application of balloon-occluded retrograde transvenous obliteration to gastric varices complicating refractory ascites. Cardiovasc Intervent Radiol. 2004;27:64–7.
12. Hirota S, Kobayashi K, Maeda H, Ymamoto S, Nakano N, Balloon-occluded retrograde transvenous obliteration for portal hypertension. Radiat Med. 2006;24:315–20.
13. Masaki M, Obara K, Suzuki S, et al. The destructive effects of sclerosant ethanolamine oleate on mammalian vessel endothelium. Gastroenterol Jpn. 1990;25:230–5.
14. Saad WE, Anderson CL, Patel RS, et al. Management of gastric varices in the pediatric population with balloon-occluded retrograde transvenous obliteration (BRTPO) utilizing sodium tetradecyl sulfate foam sclerosis with or without partial splenic artery embolization. Cardiovasc Intervent Radiol. 2015;38:236–41.
15. Miyoshi H, Oshiba S, Matsumoto A, Takada K, Umegaki E, Hirata I. Haptoglobin prevents renal dysfunction associated with intravariceal infusion of ethanolamine oleate. Am J Gastroenterol. 1991;86:1638–41.
16. Lee JY, Moon SH, Lee SM, et al. A case of noncardiogenic pulmonary edema by ethanolamine oleate. Korean J Intern Med. 1994;9:125–7.
17. Uchibori S. Pulmonary circulatory disturbance following endoscopic injection sclerotherapy. Nippon Kyobu Shikkan Gakkai Zasshi. 1993;31:833–9.
18. Saad WE, Simor PO Jr, Rose SC. Balloon-occluded retrograde transvenous obliteration of gastric varices. Cardiovasc Intervent Radiol. 2014;37:299–315.
19. Gwon DI, Ko GY, Yoon HK, et al. Gastric varices and hepatic encephalopathy: treatment with vascular plug and gelatin sponge-assisted retrograde transvenous obliteration—a primary report. Radiology. 2013;268(1):281–7.
20. Kim YH, Kim HY, Kim CS, Kang UR, Kim SH, Kim JH. Comparison of balloon-occluded retrograde transvenous obliteration (BRTO) using ethanolamine oleate, BRTO using sodium tetradecyl sulfate foam and vascular plug-assisted retrograde transvenous obliteration (PARTO). Cardiovasc Intervent Radiol. 2016;39:840–6.
21. Tsurusaki M, Sugimoto K, Matsumoto S, Izaki K, Fukuda T, Akasak Y, Fujii M, Hirota S, Sugimura K. Bleeding duodenal varices successfully treated with balloon-occluded retrograde transvenous obliteration (B-RTO) assisted by CT during arterial portography. Cardiovasc Intervent Radiol. 2006;29(6):1148–51.
22. Zamora CA, Sugimoto K, Tsurusaki M, Izaki K, Fukuda T, Matsumoto S, Kuwata Y, Kawasaki R, Taniguchi T, Hirota S, Sugimura K. Endovascular obliteration of bleeding duodenal varices in patients with liver cirrhosis. Eur Radiol. 2006;16(1):73–9.

Chapter 39
Interventional Radiology: Transjugular Retrograde Obliteration

Fumio Chikamori

Abstract The method of transvenous retrograde obliteration is divided into two approaches. One is the transjugular approach and the other is the transfemoral approach. The former is called transjugular retrograde obliteration (TJO) and the latter balloon-occluded retrograde transvenous obliteration (B-RTO). TJO makes it easier than B-RTO to reach gastric varices with gastrorenal shunt (GRS) with either superselective or selective access. The gastric varices are successfully eradicated by TJO. However, TJO obliterates the GRS, which has an abundant blood flow and increased portal venous pressure. Partial splenic embolization (PSE) has the effect of decreasing splenic blood flow and portal venous pressure. The combined therapy using TJO and PSE for gastric varices is more effective than TJO only in the long-term prevention of esophageal varices after TJO.

Keywords Transjugular retrograde obliteration · Partial splenic embolization
Gastric varices · Gastrorenal shunt

39.1 Introduction

Transvenous retrograde obliteration has recently become the treatment of choice for gastric varices with gastrorenal shunt (GRS) at many institutions in Japan [1–4]. The method of transvenous retrograde obliteration is divided into two approaches. One is the transjugular approach and the other is the transfemoral approach. The former is called transjugular retrograde obliteration (TJO) [3] and the latter balloon-occluded retrograde transvenous obliteration (B-RTO) [4]. Here, we describe TJO and the combined therapy using partial splenic embolization (PSE).

F. Chikamori
Department of Surgery, Tano Hospital, Kochi, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_39

39.2 Merits

Olson et al. [5] reported a case of gastric varices treated with retrograde obliteration of esophagogastric varices with absolute ethanol and coils via the GRS through femoral vein. Kanagawa et al. [1] also reported variceal obliteration with 5% ethanolamine oleate with iopamidol (5% EOI) with the same route, but they used 40 mL of 5% EOI. Our method of TJO approaches the GRS through a jugular vein (Table 39.1). This route is easier than the femoral one to reach at the GRS with either superselective or selective access. Because absolute ethanol has stronger potency to obliterate the vein than 5% EOI, it was used to obliterate the communicating routes of GRS such as inferior phrenic and/or azygos veins. By using absolute ethanol, we could reduce the volume of 5% EOI as compared with the report of Kanagawa et al. [1]. However, the volume of absolute ethanol should be smaller, because it causes epigastric pain. Therefore, superselective access is more desirable than selective access because the required volume of absolute ethanol is smaller. The quantity of 5% EOI used should be less than 0.5 mL/kg because larger volumes can cause renal injury or lung congestion [6]. With our method, the volume is smaller than 0.3 mL/kg.

39.3 Treatment Procedure

Pentazocine 15 mg and hydroxyzine hydrochloride 25 mg are injected intramuscularly 30 min prior to the operation. Through the right internal jugular vein, we inserted an 8-French long cobra-shaped sheath into the left renal vein. We then inserted a 5- or 6-French angiographic catheter, with an occlusive balloon of 11 or 20 mm in diameter, into the GRS through a previously inserted sheath. The balloon is inflated with 0.7–4.0 mL of diluted contrast medium to stop the blood flow in the GRS (Fig. 39.1). The communicating routes of the GRS, such as the inferior phrenic and/or retroperitoneal veins, are obliterated with a microcoil when a 3-French microcatheter can be inserted into these veins and/or with absolute ethanol when the microcatheter cannot be inserted. After the procedure, gastric variceal blood flow is completely controlled, and we inject 5–20 mL of 5% EOI into the gastric varices

Table 39.1 Techniques of retrograde obliteration for gastric varices

Method	Author	Approach	Embolic material	Duration of Balloon inflation
Transrenal-vein reflux ethanol sclerosis	Olson (1984)	Femoral v.	Ethanol coil	None
Balloon-occluded retrograde transvenous obliteration (B-RTO)	Kanagawa (1991)	Femoral v.	5%EOI	30 min
Transjugular retrograde obliteration (TJO)	Chikamori (1992)	Jugular v.	Ethanol coil 5%EOI	24 h

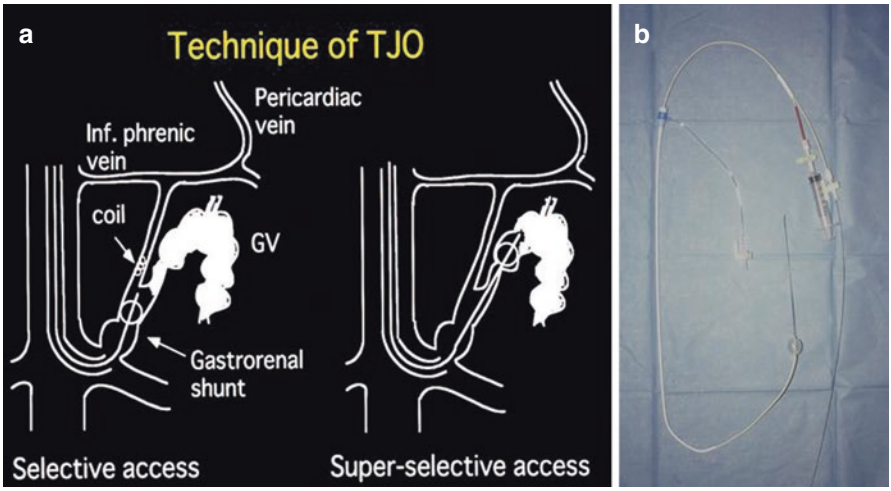


Fig. 39.1 (**a**) Schematic diagram of TJO. (**b**) Long, cobra-shaped sheath and angiographic catheter with an occlusive balloon

under fluoroscopy. After confirming the presence of thrombi in the gastric varices by retrograde shunt venography the next day, we remove the catheter. If retrograde shunt venography reveals no thrombi in the varices, we repeat the procedure. The catheter is left in the vein for 1 or more days, depending on how rapidly the thrombi form in the gastric varices [3].

39.4 Results

We reported on 8 years of experience with TJO performed on 54 patients with gastric varices [7]. The success of obliteration of the gastric varices was confirmed by enhanced computed tomography (CT) 1 week, 1 month, and 3 months after TJO. The gastric varices were successfully obliterated by TJO in all patients. Eradication of the gastric varices was diagnosed by endoscopic examination 1 week, 1 month, and 3 months after TJO. The gastric varices were successfully eradicated by TJO in all patients.

Minor complications observed were fever more than 38 °C in 20 patients, hemoglobinuria in 8, pleural effusion in 3, ascites which could be controlled with diuretics in 1, and hemorrhagic gastritis in 3. There was no deterioration in liver function.

There was no recurrence or bleeding of gastric varices in any patient after TJO.

The overall cumulative survival rate of patients after TJO was 92% at 1 year, 76% at 3 years, 61% at 5 years, and 47% at 8 years. The cumulative survival rate of patients without HCC after TJO was 88% at l year, 82% at 3 years, 73% at 5 years, and 60% at 8 years. The cumulative survival rate of patients with HCC after TJO

was 100% at 1 year, 64% at 3 years, and 21% at 5 years. Patient survival differed depending on whether or not HCC was present ($p < 0.05$).

The cumulative occurrence rate of esophageal varices in patients in whom the inferior phrenic vein was preserved after TJO was 30% at 1 year, 51% at 3 years, and 63% at 5 years. The cumulative occurrence rate of esophageal varices in patients in whom the inferior phrenic vein was not preserved after TJO was 36% at 1 year, 56% at 3 years, and 56% at 5 years (Fig. 39.4). The occurrence rate of esophageal varices after TJO was not affected by the preservation of the inferior phrenic vein. Esophageal varices that occurred after TJO were treated by EIS using the Takase method.

39.5 Effects on Portal Hemodynamics

We investigated the short-term effects on portal hemodynamics of TJO in 30 patients with gastric varices with GRS [8]. The portal blood flow was measured by an ultrasonic duplex Doppler system, and the wedged hepatic venous pressure was measured by hepatic venous catheterization, before and after TJO. The wedged hepatic venous pressure was significantly increased the day after TJO compared with that before therapy (257 ± 71 vs. 307 ± 73 mmH_2O, $p < 0.01$). The portal venous flow was significantly increased 1 week after TJO compared with that before therapy (744 ± 190 vs. 946 ± 166 mL/min, $p < 0.01$). The serum albumin levels before and after TJO were 3.0 ± 0.4 and 3.1 ± 0.5 g/dL, respectively, and the total bilirubin levels were 1.5 ± 0.7 and 1.5 ± 0.8 mg/dL, respectively, neither of these parameters changing significantly. The plasma ammonia levels before and after TJO were 109 ± 62 and 67 ± 31 μg/dL, and the indocyanine green retention rates at 15 min were 31 ± 13 and 24 ± 13%, both showing a significant change ($p < 0.01$ and $p < 0.05$, respectively). We conclude that TJO increases portal blood flow which contributes to the decrease in plasma ammonia levels and the indocyanine green retention rate but increases the wedged hepatic venous pressure.

39.6 Combined Therapy Using PSE

Our previous study [8] showed that TJO obliterates the GRS, which has an abundant blood flow, and increases portal venous pressure. PSE has the effect of decreasing splenic blood flow and portal venous pressure [9]. Therefore, we recommend the combined therapy using PSE.

PSE was performed 7–14 days before TJO. Through the right femoral artery, a 5- French catheter was selectively advanced to the splenic artery. Through this catheter, a 3-French microcatheter was positioned into the peripheral splenic artery, distal to the great pancreatic artery. After selective splenic arteriography, more than

70% splenic arterial embolization was performed using platinum microcoils and/or gelatin sponge under fluoroscopy.

Between November 2002 and December 2006, 14 patients with gastric varices with GRS were treated by combining TJO and PSE (group 1) [10]. These patients were compared with 19 patients with gastric varices with GRS treated by only TJO (group 2) for the disappearance rate of gastric varices, the cumulative survival rate, and the occurrence rate of esophageal varices after TJO. The disappearance rate of gastric varices following TJO was 100% in both groups. The 3-year cumulative survival rate after TJO was 92% in group 1 and 95% in group 2. The 3-year cumulative occurrence rate of esophageal varices after TJO was 9% in group 1 and 45% in group 2, with a significant difference ($p < 0.05$). We conclude that the combination of TJO and PSE for gastric varices is more effective than TJO only in the long-term prevention of esophageal varices after TJO.

39.7 Case Report

A 54-year-old man with liver cirrhosis was admitted for the treatment of large gastric varices (Fig. 39.2a, b). The Child-Pugh score was grade B. Antibodies to hepatitis B was positive. This case was treated by PSE and TJO. Splenic arterial portography showed that the gastric varices were supplied by the posterior gastric vein and drained into the GRS (Fig. 39.3a). At first, PSE was performed using microcoils and gelatin sponge. Two weeks after PSE, TJO was performed. Retrograde shunt venography showed the inferior phrenic veins; however, gastric varices were unclear (Fig. 39.3b). After embolization of inferior phrenic vein with 5 mL of ethanol and 80 mL of 50% glucose, 10 mL of 5% EOI was injected into the gastric varices (Fig. 39.3c). CT 1 week after TJO revealed the gastric varices had

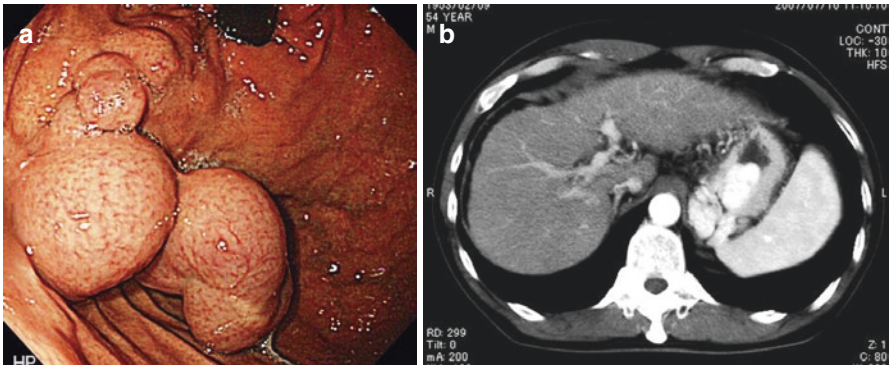


Fig. 39.2 (**a**) Endoscopic picture before TJO showing large gastric varices. (**b**) CT before PSE and TJO showing large gastric varices and mild splenomegaly

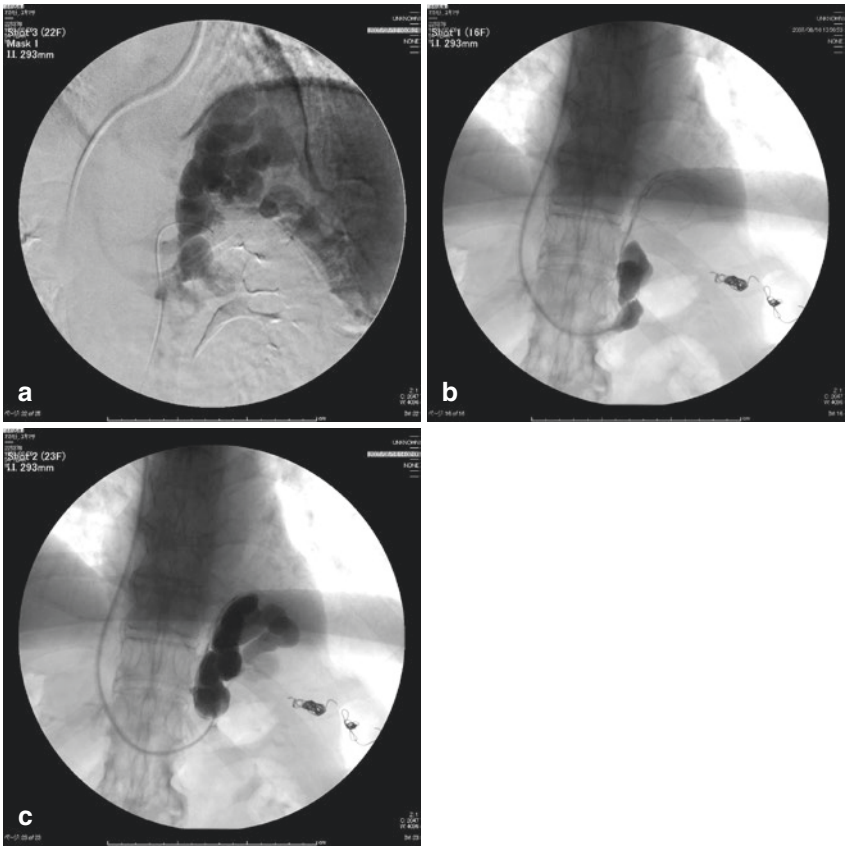


Fig. 39.3 (**a**) Splenic arterial portogram showing that the gastric varices are supplied by the posterior gastric vein and drained into the GRS. (**b**) Retrograde shunt venogram shows inferior phrenic vein; however, gastric varices are unclear. (**c**) After embolization of inferior phrenic vein with 5 mL of ethanol and 80 mL of 50% glucose, 10 mL of 5% EOI was injected into the gastric varices

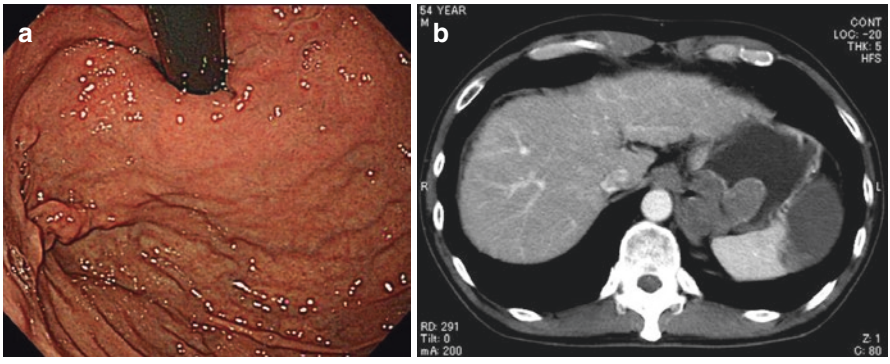


Fig. 39.4 (**a**) CT 1 week after TJO showing that the gastric varices are completely obliterated by the thrombi. (**b**) Endoscopic picture 3 months after PSE and TJO showing that the gastric varices are eradicated

been completely obliterated by thrombi (Fig. 39.4a). Endoscopy 3 months after TJO proved the gastric varices had been eradicated (Fig. 39.4b).

Acknowledgments I thank Dr. Niranjan Sharma PhD, Mornington Health Centre, Dunedin, New Zealand, for his helpful comments.

References

1. Kanagawa H, Mima S, Kouyama H, Mizuno H, Iziri M, Tanabe T, et al. A successfully treated case of fundic varices by retrograde transvenous obliteration with balloon (in Japanese). Jpn J Gastroenterol. 1991;88:1459–62.
2. Chikamori F, Aoyagi H, Shibuya S, Takase Y. Indication of injection sclerotherapy for gastric varices based on percutaneous transhepatic portography (in Japanese). Gastroenterol Endosc. 1992;34:29–36.
3. Kanagawa H, Mima S, Kouyama H, Gotoh K, Uchida T, Okuda K. Treatment of gastric fundal varices by balloon-occluded retrograde obliteration. Gastroenterol Hepatol. 1996;11:51–8.
4. Chikamori F, Shibuya S, Takase Y, Ozaki A, Fukao K. Transjugular retrograde obliteration for gastric varices. Abdom Imaging. 1996;21:299–303.
5. Olson E, Yune HY, Klatie EC. Transrenal-vein reflux ethanol sclerosis of gastroesophageal varices. AJR. 1984;143:627–8.
6. Yoshida T. The safety and the mechanism of action of ethanolamine oleate used in injection sclerotherapy (in Japanese). Gastroenterol Endosc. 1986;28:1491–503.
7. Chikamori F, Kuniyoshi N, Shibuya S, Takase Y. Eight years of experience with transjugular retrograde obliteration for gastric varices with gastrorenal shunts. Surgery. 2001;129:414–20.
8. Chikamori F, Kuniyoshi N, Shibuya S, Takase Y. Short-term portal hemodynamic effects of transjugular retrograde obliteration of gastric varices with gastrorenal shunts. Dig Surg. 2000;17:332–6.
9. Chikamori F, Kuniyoshi N, Shibuya S, Takase Y. Short-term portal hemodynamic effects of partial splenic embolization for hypersplenism. Hepatogastroenterology. 2007;54:1847–9.
10. Chikamori F, Kuniyoshi N, Kawashima T, Takase Y. Gastric varices with gastrorenal shunt: combined therapy using transjugular retrograde obliteration and partial splenic embolization. AJR. 2008;191:555–9.

Chapter 40
Interventional Radiology: Percutaneous Transhepatic Obliteration and Transileocolic Obliteration

Hiroshi Yoshida, Hiroshi Makino, Tadashi Yokoyama, Hiroshi Maruyama, Atsushi Hirakata, Junji Ueda, Hideyuki Takata, Yasuhiro Mamada, Nobuhiko Taniai, and Eiji Uchida

Abstract Transportal obliteration is a technique used in portal hypertension to embolize the collateral veins of the portal system. It is used to treat refractory esophagogastric varices, ectopic varices, or portal-systemic encephalopathy. After insertion of a 5-French long sheath introducer into the portal vein, a catheter is inserted directly into the vein, and the portal circulation is visualized by portography. A balloon catheter is inserted selectively into the inflow site of the veins feeding the varices. Sclerosant is injected to obliterate the feeding vein or veins, and steel coils are used to complete the obliteration. However, the rate of complete disappearance of varices is not high after transportal obliteration alone. Transportal obliteration combined with endoscopic treatment or balloon-occluded retrograde transvenous obliteration, or both, is useful for treating uncontrolled bleeding from varices. The most frequent complication of percutaneous transhepatic obliteration is intraperitoneal bleeding. Severe coagulopathy is a contraindication for both percutaneous transhepatic obliteration and transileocolic vein obliteration, and ascites is a contraindication for percutaneous transhepatic obliteration. The presence of collateral veins decreases portal venous pressure. Obliteration of these veins by transportal obliteration thus increases portal congestion and portal pressure, especially in patients with cirrhosis. Partial splenic embolization has been performed incrementally to reduce portal venous pressure to the level it was before obliteration of the collateral veins. Transportal obliteration in combination with endoscopic treatment or with other forms of interventional radiology is useful for treating refractory esophagogastric varices, ectopic varices, or portal-systemic encephalopathy.

H. Yoshida (✉) · Y. Mamada · E. Uchida
Department of Surgery, Nippon Medical School, Tokyo, Japan
e-mail: hiroshiy@nms.ac.jp

H. Makino · T. Yokoyama · H. Maruyama · A. Hirakata · J. Ueda · H. Takata
Department of Surgery, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan

N. Taniai
Department of Surgery, Nippon Medical School Musashi Kosugi Hospital, Tokyo, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_40

Keywords Esophagogastric varices · Interventional radiology (IVR) · Transportal obliteration

40.1 Introduction

There are various modalities for the treatment of portal hypertension. Recently, endoscopic techniques have been developed and have become the treatments of first choice for esophagogastric varices. However, interventional radiology (IVR) is required for treating refractory cases. In this paper, we review transportal obliteration for the treatment of portal hypertension.

40.2 IVR

IVR techniques for the treatment of esophagogastric varices were developed in the 1970s [1]. Recently, IVR has been used to treat various complications of portal hypertension. IVR techniques used for esophagogastric varices include transportal obliteration, balloon-occluded retrograde transvenous obliteration (BRTO), partial splenic embolization (PSE), and transjugular intrahepatic portosystemic shunt (TIPS). Before IVR is performed, the portal hemodynamics should be evaluated. Angiography can be used to assess the hemodynamics of varices during embolization. Transportal obliteration and BRTO are used to embolize the collateral veins of the portal system in cases of portal hypertension. These IVR techniques both increase portal pressure. PSE reduces inflow of the portal system, whereas TIPS increases outflow of the system. The IVR techniques such as PSE and TIPS reduce portal pressure.

40.3 Transportal Obliteration

Catheterization of the portal venous system can be used to measure portal venous pressure, portal blood velocity, and portal blood flow volume. The portal venous system can be catheterized via liver puncture, by recanalization of the umbilical vein, via the transjugular–transhepatic route, or through the transileocolic vein.

We mainly use two methods to obliterate hepatofugal veins branching from portal system: percutaneous transhepatic obliteration (PTO) and transileocolic vein obliteration (TIO). These procedures are performed in similar ways.

40.3.1 Indications for Transportal Obliteration

Transportal obliteration in combination with endoscopic treatment or with other forms of IVR is useful for treating refractory esophagogastric varices, ectopic varices, or portal-systemic encephalopathy.

40.3.2 Treatment Procedure

In PTO, the lateral approach ensures a long puncture canal through the liver with reduced risk of bleeding. After ultrasonographic examination, local anesthetic is infiltrated into the skin, subcutaneous tissue, and parietal peritoneum. A distal to second-order branch of the portal vein is punctured with a 19-gauge needle under ultrasonographic guidance. After the puncture, a guidewire is inserted into the portal vein under fluoroscopic control. A 5-French long sheath introducer is inserted, and a catheter is then placed directly into the portal vein, and the portal circulation is visualized by portography. The collateral vein system that develops in portal hypertension can be visualized by selective portography. The most common collateral vein systems arise from the left gastric vein (coronary vein) and short gastric vein. For routine portography, the tip of the catheter is placed in the splenic vein. A balloon catheter is inserted selectively into the inflow site of the veins feeding the varices. The balloon is inflated, and a test dose of contrast medium is injected to determine the optimal volume of sclerosant. Five percent ethanolamine oleate with iopamidol, 50% glucose, or both are injected to obliterate the feeding vein or veins. Steel coils are then used to complete the obliteration [2] (Fig. 40.1). To prevent bleeding or bile duct leakage after retraction of the catheter, the puncture canal should be plugged with gelatin sponge.

In TIO [3], a right transrectal incision is made under epidural anesthesia. The transileocolic vein is divided and isolated and punctured with a 19-gauge needle. After ligation of the proximal transileocolic vein, a guidewire is inserted into the portal vein, and a 5-French sheath introducer is inserted (Fig. 40.2). The obliteration technique is the same as for PTO. To prevent bleeding, the distal transileocolic vein is ligated after removal of the catheter sheath.

40.3.3 Complications

The most frequent complication in PTO is intraperitoneal bleeding caused by accidental penetration of the liver hilum, failure to plug the puncture canal after the puncture, or severe coagulopathy [1]. In TIO, adhesion of the ileum occasionally occurs.

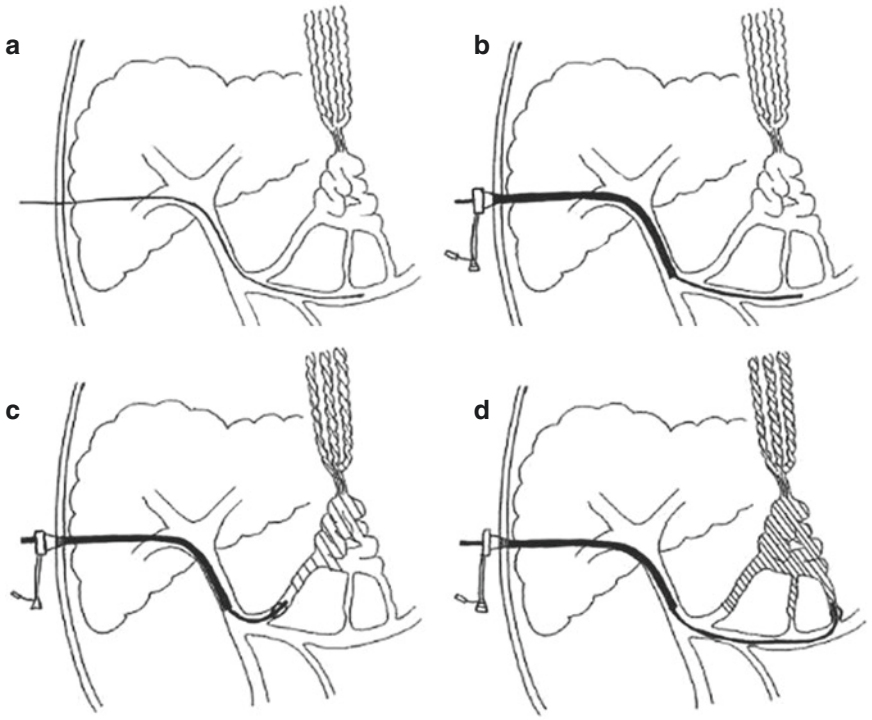


Fig. 40.1 Percutaneous transhepatic obliteration. (**a**) A guidewire is inserted into the portal vein under fluoroscopic control. (**b**) After a 5-French long sheath introducer is inserted, a catheter is inserted directly into the portal vein, and the portal circulation is visualized by portography. (**c**) and (**d**) A balloon catheter is inserted selectively into the inflow site of the veins feeding the varices

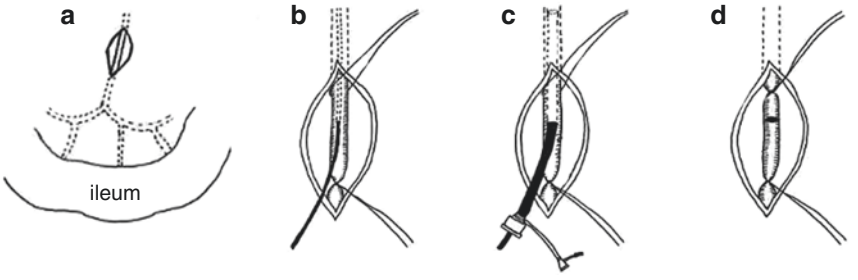


Fig. 40.2 Transileocolic vein obliteration. (**a**) The transileocolic vein is divided and isolated. (**b**) A 19-gauge needle is used to puncture the transileocolic vein. After ligation of the proximal transileocolic vein, a guidewire is inserted into the portal vein. (**c**) A 5-French sheath introducer is inserted. (**d**) The distal transileocolic vein is ligated after removal of the catheter sheath

40.3.4 Contraindications

Severe coagulopathy is a contraindication for PTO and TIO, and ascites is a contraindication for PTO.

40.4 Combination with IVR

Transportal obliteration is highly effective for treating gastric or ectopic varices, because the veins feeding the varices are obliterated. However, the rate of complete disappearance of gastric varices is not high after transportal obliteration alone. Transportal obliteration combined with BRTO is useful for treating uncontrolled bleeding from gastric or ectopic varices. Transportal obliteration is also effective for treating portal-systemic encephalopathy.

The presence of collateral veins, including the veins feeding gastric varices, decreases portal venous pressure. Obliteration of collateral veins by using such procedures as BRTO and transportal obliteration increases portal congestion and portal pressure, especially in patients with cirrhosis. PSE has been performed incrementally to reduce portal venous pressure to the level it was before obliteration of the collateral veins [2, 4, 5].

Combination of these IVR techniques is useful for treating esophagogastric varices, ectopic varices, or portal-systemic encephalopathy.

40.5 Combination of Endoscopic Treatment with IVR

Treatment of gastric varices solely with endoscopic modalities or IVR is occasionally inadequate. Our group has previously reported that treatment combining IVR and endoscopic modalities significantly decreases the risk of long-term rebleeding and retreatment rates in patients with esophagogastric varices [2]. This combination was shown to be effective for treating esophagogastric varices, especially in patients with poor liver function [2, 6].

40.6 Conclusion

Transportal obliteration in combination with endoscopic treatment or with other forms of IVR is useful for treating refractory esophagogastric varices, ectopic varices, or portal-systemic encephalopathy.

References

1. Lunderquist A, Vang J. Transhepatic catheterization and obliteration of the coronary vein in patients with portal hypertension and esophageal varices. N Engl J Med. 1974;291:646–9.
2. Taniai N, Onda M, Tajiri T, Yoshida H, Mamada Y. Combined endoscopic and radiologic intervention to treat esophageal varices. Hepatogastroenterology. 2002;49:984–8.
3. Nakayama H, Masuda H, Miyake H, Amano S, Fukuzawa M. Prophylactic transileocolic obliteration of esophageal varices after balloon-occluded retrograde transvenous obliteration of gastric varices with a gastrorenal shunt. Hepatogastroenterology. 2003;50:1411–4.
4. Hirota S, Ichikawa S, Matsumoto S, Motohara T, Fukuda T, Yoshikawa T. Interventional radiologic treatment for idiopathic portal hypertension. Cardiovasc Intervent Radiol. 1999;22:311–4.
5. Chikamori F, Kuniyoshi N, Kawashima T, Shibuya S, Takase Y. Combination treatment of partial splenic embolization, endoscopic embolization and transjugular retrograde obliteration for complicated gastroesophageal varices. Hepatogastroenterology. 2004;51:1506–9.
6. Yoshida H, Mamada Y, Taniai N, Tajiri T. New methods for the management of gastric varices. World J Gastroenterol. 2006;12:5926–31.

Chapter 41
Interventional Radiology: Transjugular Intrahepatic Portosystemic Shunt

Shozo Hirota

Abstract TIPS (transjugular intrahepatic portosystemic shunt) is a percutaneous procedure for forming a new intrahepatic shunt in which the hepatic vein connects to the portal vein. Portal venous blood flows out through this shunt resulting in a decrease in the portal pressure. TIPS was first reported by Dr. Rosch in 1969 and clinically applied with metallic stent in 1989. Since then TIPS has been widely performed in the USA and Europe. Indications for TIPS include refractory esophageal varices, refractory ascites, and portal hypertensive gastropathy. From the laboratory data, less than 18 of MELD score are recommended for indication. In Japan, TIPS is not approved by the Ministry of Health, Labour and Welfare, so it has not been performed widely.

Keywords Portal decompression · Esophageal varices · Refractory ascites · Portal hypertensive gastropathy

41.1 Introduction

TIPS (transjugular intrahepatic portosystemic shunt) is a percutaneous procedure for forming a new intrahepatic shunt in which the hepatic vein connects to the portal vein. Portal venous blood flows out through the shunt resulting in a decrease of the portal pressure. This principle is the same as the surgical shunt operation, but TIPS is performed less invasively. The idea of TIPS was first reported by Rosch et al. [1] in 1969, and experimental data was reported. In 1982, Colapinto et al. [2] reported the first clinical case of TIPS using balloon dilatation of shunt tract. However, the result of this method showed shunt obstruction in the short term. In 1989 Richter et al. [3] applied an expandable metallic stent over the new shunt to maintain the

S. Hirota (✉)
IVR Center, Konan Hospital, Kobe, Hyogo, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_41

portovenous flow, showing widely acceptable results. After that, TIPS has been widely performed for esophageal variceal bleeding in Western countries. In Japan, Yamada et al. [4] and Nakamura et al. [5] reported the first clinical report of TIPS. However, TIPS has not yet been approved by the Ministry of Health, Labour and Welfare (MHLW) in Japan.

41.2 Method

Preoperative imaging diagnosis is important in deciding the direction and the distance of needle puncture from the hepatic vein to the portal vein. Contrast-enhanced 3D-CT angio is useful for confirming the relationship of the hepatic vein and the portal vein [6–8].

First, a 10Fr TIPS guiding catheter is inserted to the right hepatic vein via the right jugular vein which is punctured under ultrasonographic guidance (Fig. 41.1). Next, a TIPS needle-catheter set is inserted through the 10Fr guiding sheath. The authors usually used a Rosch-Uchida TIPS set (Cook Inc. Bloomington, IN. USA) which consists of a J-shaped 10Fr guiding sheath, a 14G stiffening metal cannula, 5Fr catheter, and a trocar stylet (needle). The right posterior branch of the portal

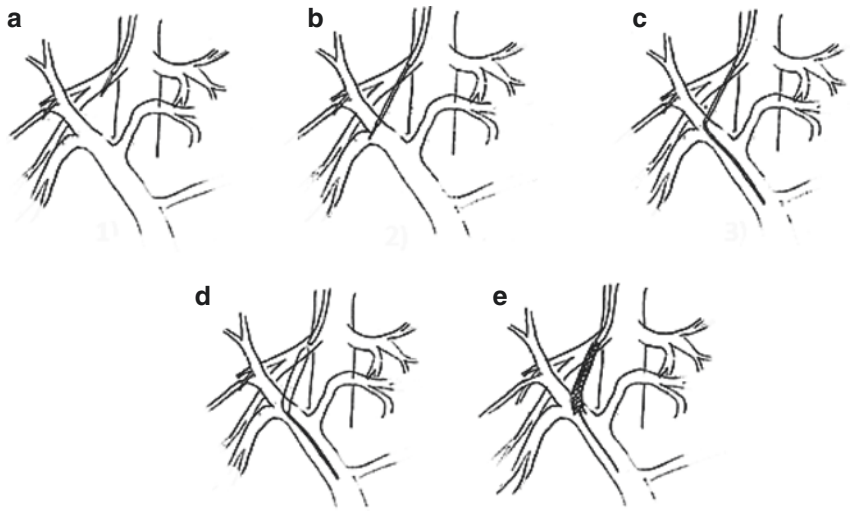


Fig. 41.1 (**a**) A 10Fr guiding catheter is introduced to the right hepatic vein via transjugular approach. (**b**) A stylet needle is punctured to the right posterior portal vein, and a guidewire is introduced into the portal vein trunk. (**c**) A 5Fr catheter is inserted over the guidewire. Then, a 10Fr guiding catheter is inserted over the wire into the portal trunk. (**d**) A balloon catheter is introduced to the shunt tract and is dilated in the shunt. (**e**) An expandable metallic stent is deployed over the shunt

vein is punctured from the right hepatic vein using a needle within a 5Fr catheter. After withdrawal of the needle, the 5Fr catheter is withdrawn until suction of blood is confirmed. When the blood is aspirated, we inject the contrast media to confirm the catheter be in the right portal branch. A 0.038 in. guidewire is inserted to the portal vein trunk via the right portal vein, and the 5Fr catheter is advanced over the wire into the portal vein trunk. Next, a 10Fr guiding catheter is advanced over the 5Fr catheter to the portal vein trunk. Portal venography should be taken to confirm the entry and reentry point of the shunt. An 8 mm diameter balloon angioplasty catheter is advanced through the 10Fr guiding catheter, and the shunt tract is dilated by inflation of the balloon. Two entry points namely from the hepatic vein to the parenchyma and from the parenchyma to the portal vein are depicted as the "waist" appearance of the balloon during inflation. The waist portion is dilated until the waist disappears (Fig. 41.2). The distance between the two "waist" portions is measured to make the right choice of the metallic stent. An expandable metallic stent with 10 mm diameter (SMART control stent, Cordis Health Care Japan, Tokyo) is placed over the shunt. After placement of the stent, post-stenting balloon dilatation is performed. In the USA and the EU nations, Viatorr (ePTFE-linked stent graft) is available [9]. In Japan, a metallic bare stent and a Viatorr stent are not approved for portal vein use by the MHLW.

Finally, direct portography is taken to confirm the shunt patency and the shunt diameter. Portal pressure at the portal trunk and the right hepatic vein is measured. The pressure gradient between the right atrium and portal vein trunk should be lower than 15 mmHg.

41.3 Indication

41.3.1 Esophageal Varices

Although initially TIPS was applied to the acute esophageal bleeding, these days endoscopic treatment is performed as the first-line treatment for esophageal varices. In Japan, TIPS has been indicated only for the esophageal varices refractory to the endoscopic treatment [8, 9].

41.3.2 Gastric Varices

The portal pressure of patient with gastric varices is not very high because of the presence of the portosystemic shunts such as the gastrorenal venous shunt or the gastrophrenic venous shunt. Therefore, additional shunt creation by TIPS does not function effectively. The success rate of stoppage of bleeding of gastric varices is reported to be about 50%. In Japan, TIPS is not indicated for gastric varices [10].

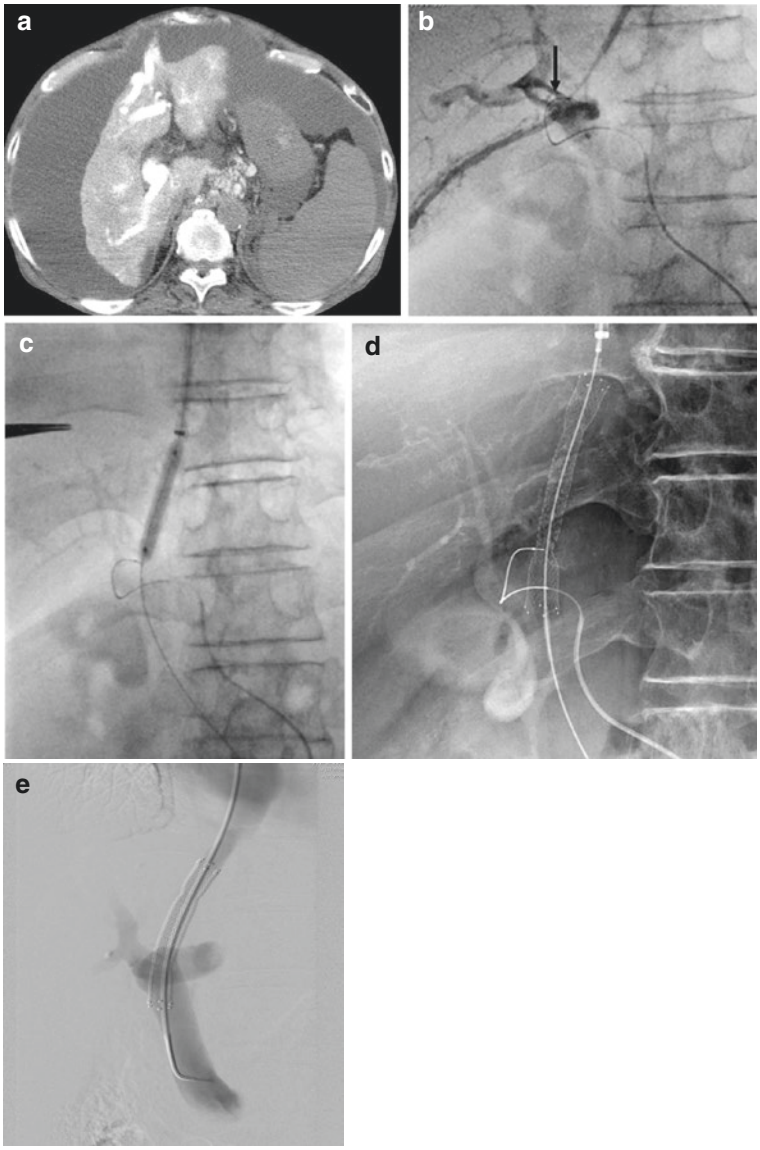


Fig. 41.2 A 73-year-old man with refractory ascites due to alcoholic cirrhosis. (**a**) Massive ascites and atrophic liver are shown on CT. (**b**) Hepatic arteriography was performed before TIPS procedure. The guidewire was placed in the part just passing the right posterior arterial branch (*arrow*) as a landmark because the posterior portion of the artery was located anterior to the posterior portal branch. After the puncture to the right posterior portal branch, test injection of contrast media showed the catheter was inside the right portal branch. (**c**) Then guidewire was advanced into the portal trunk, and tract was dilated by balloon inflation with 6 mm in diameter. (**d**) After dilatation of the tract, a bare metallic stent with 8 mm in diameter was placed between the right hepatic artery and the right portal branch. (**e**) Direct portography via the catheter through TIPS tract was taken. Portosystemic shunt is clearly seen

41.3.3 Refractory Ascites

Patients with refractory ascites are usually maintained with a diuretic drug, hypochloric diet, peritoneal paracentesis, cell-free and concentrated ascites reinfusion therapy (CART), or peritoneal venous shunting (Denver shunt). But massive ascites makes it difficult for the patients to maintain an active daily life. These patients are indicated for TIPS [11]. Moreover, patients with a MELD-Na score less than 18 points are also indicated. Nakamura et al. [5] reported the response rate, which means the disappearance of ascites or a status with no need of paracentesis was 63% in 43 patients (Child class B, 18 patients.; class C, 25 patients).

41.3.4 Portal Hypertensive Gastropathy (PHG)

Portal hypertensive gastropathy means congestion of gastric mucosa brought on by portal hypertension and causing diffuse hemorrhage. TIPS is indicated for patients PHG which is uncontrollable with diuretic drugs or endoscopic therapy.

41.3.5 Portal Thrombosis

Portal thrombosis refractory to anticoagulation therapy may be indicated. Restoring hepatopetal portal flow by TIPS may shrink the portal thrombus.

41.3.6 Indication from the Laboratory Data

Severe hepatic fibrosis is not indicated for TIPS because it may induce hepatorenal syndrome. From the view point of hepatic function reserve, TIPS is indicated for patients with serological data as below: (1) total bilirubin <3.0 mg/dL, (2) S-Cr < 2.0 mg/dL, and (3) MELD-Na score < 18.

41.4 Contraindication

Absolute contraindications are as follows: (1) severe progressive liver failure, (2) severe encephalopathy, and (3) heart failure.

Relative contraindications are considered to be as follows: (1) regional portal thrombus, (2) hepatocellular carcinoma, (3) diffuse cystic liver disease, and (4) biliary obstruction.

41.5 Results

There are many reports of clinical results of TIPS. The technical success rate is reported to be more than 95% [12]. For esophageal varices, the hemostatic response rate was 88%, and the rebleeding rate was 19%, while it was 47% in cases treated by endoscopic therapy.

For hemostatic response, the rate of gastric varices is reported to be 56% for TIPS and 91% for TIPS combined with BRTO. For refractory ascites, the response rate after TIPS was reported to be 63% [11].

Periprocedural complications of TIPS include stent malposition, hemobilia, and hepatic artery puncture. Postprocedural complications were reported by LaBerge et al. [13] saying hepatic encephalopathy occurred in 52 out of 247 patients accounting for 21%. But most of the patients are controlled by conservative medical treatment. Recurrent portal hypertension and recurrent bleeding after TIPS were reported [14]. Shunt stenosis or thrombosis is a major cause of these complications. For shunt stenosis, balloon angioplasty is necessary, and thrombolysis or balloon dilatation is a means for thrombosis.

Over all survival rates after TIPS creation were reported: 81.4% (1 year), 70.6% (2 years), and 70.6% (3 years). These are survival rates according to the Child's classification: Child A, 88.5% (1 year), 77.5% (2 years), and 77.5% (3 years); Child B, 80.1% (1 year), 70.1% (2 years), and 70.1% (3 years); and Child C, 65.3% (1 year), 54.2% (2 years), and 38.4% (3 years).

41.6 Comparison of BRTO and TIPS for Portal Hypertension

For isolated gastric varices, there are some current scientific papers comparing the efficacy of both BRTO and TIPS. One researcher says that BRTO was proved more effective than TIPS in hemostasis of gastric variceal bleeding, associated with significantly less risk of rebleeding [15, 16]. And another researcher says that BRTO is an effective method of treating isolated gastric varices with similar outcomes and complication rates to those of TIPS with a covered stent except for a lower rate of hepatic encephalopathy [17, 18].

When the benefits of each treatment are compared, BRTO is superior to TIPS in devascularization of varices, while, TIPS is found to be superior to BRTO in the treatment of refractory ascites. In emergent cases due to active bleeding, endoscopic treatment is the first choice, and TIPS is the second choice in the case of failed endoscopic treatment. Combination treatment of TIPS and BATO (balloon-occluded antegrade transvenous obliteration) is logically excellent, but collateral vessels to the varices may develop because of antegrade obliteration [19]. However, for portosystemic shunt encephalopathy, there is little question that BRTO or shunt occlusion should be the treatment of first choice.

Precise treatment indications for performing TIPS or BRTO for portal hypertension is important. Portosystemic shunt syndrome [20] may include various negative conditions introduced by a portosystemic shunt, leading to a poor prognosis in a patient with a shunt. TIPS may lead to portosystemic shunt syndrome; therefore, we should consider the possibility of this syndrome as a sequelae while selecting the treatment method for portal hypertension [15]. The further development of BRTO is expected in future.

References

1. Rosch J, Hanafee WN, Snow H. Transjugular portal venography and radiological portosystemic shunt: an experimental study. Radiology. 1969;92:1112–4.
2. Colapinto RF, Stronell RD, Birch SJ, Langer B, Blendis LM, Greig PD, Gilas T. Creation of an intrahepatic portosystemic shunt with a Grüntzig balloon catheter. Can Med Assoc J. 1982;126(3):267–8.
3. Richter GM, Roeren T, Brado M, Nöldge G, Kauffmann GW. Long-term results after TIPSS with the Palmaz stent. Radiologe. 1994;34(4):178–82.
4. Yamada R, Koda Y, Hamuro M, Hayashi S, Nakamura K, Tanihata H, et al. Transjugulara intrahepatic portosystemic shunt: a new therapy for portal hypertension. Nihon Geka Gakkai Zasshi. 1996;97(1):83–8.
5. Nakamura K, et al. A clinical experience of transjugular intrahepatic portosystemic shunt. J Jpn Soc Gastroenterol. 1994;91:171–9.
6. Gaba RC, Khiatani VL, Knuttinen MG, Omene BO, Carrillo TC, Bui JT, et al. Comprehensive review of TIPS technical complications and how to avoid them. Am J Roentgenol. 2011;196:675–85.
7. Sanyal AJ, Freedman AM, Luketic VA, Purdum PP III, Shiffman ML, DeMeo J, et al. The natural history of portal hypertension after transjugular intrahepatic portosystemic shunts. Gastroenterology. 1997;112:889–98.
8. Haskal ZJ. Transjugular intrahepatic portosystemic shunts. In: Kandarpa K, Machan L, editors. Handbook of interventional radiologic procedures. 4th ed. Baltimore: Lippincott Williams & Wilkins; 2011. p. 390–7.
9. Tripathi D, Ferguson J, Barkell H, Macbeth K, Ireland H, Redhead DN, et al. Improved clinical outcome with transjugular intrahepatic portosystemic stent-shunt utilizing polytetrafluoroethylene-covered stents. Eur J Gastroenterol Hepatol. 2006;18:225–32.
10. Report of current state of portal hypertension in Japan edited by Japanese Society of Portal Hypertension; 1990. JSPH.
11. Rossle M, Ochs A, Gulberg V, Siegerstetter V, Holl J, Deibert P, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med. 2000;342:1701–7.
12. Burroughs AK, Vangeli M. Transjugular intrahepatic portosystemic shunt versus endoscopic therapy: randomized trials for secondary prophylaxis of variceal bleeding: an updated meta-analysis. Scand J Gastroenterol. 2002;37:249–52.
13. LaBerge JM, Ring EJ, Gordon RL, Lake JR, Doherty MM, Somberg KA, et al. Creation of transjugular intrahepatic portosystemic shunts with the wallstent endoprosthesis: results in 100 patients. Radiology. 1993;187:413–20.
14. Boyer TD, Haskal ZJ. American Association for the study of liver diseases practice guidelines:the role of transjugular intrahepatic portosystemic shunt creation in the management of portal hypertension. J Vasc Interv Radiol. 2005;16:615–29.

15. Hirota S, Kobayashi K, Kako Y, Takaki H, Yamakado K. Balloon-occluded retrograde transvenous obliteration of varices: focusing on the portal hemodynamics and the recent techniques. Hepatol Int. 2018;12:102–11. https://doi.org/10.1007/s12072-017-9813-2.
16. Kim SK, Lee KA, Sauk S, Korenblat K. Comparison of transjugular intrahepatic portosystemic shunt with covered stent and balloon-occluded retrograde transvenous obliteration in managing isolated gastric varices. Korean J Radiol. 2017;18(2):345–54.
17. Lee SJ, Kim SU, Kim MD, Kim YH, Kim GM, Park SI, Won JY, Lee DY, Lee KH. Comparison of treatment outcomes between balloon-occluded retrograde transvenous obliteration and transjugular intrahepatic portosystemic shunt for gastric variceal bleeding hemostasis. J Gastroenterol Hepatol. 2017;32:1487–94. https://doi.org/10.1111/jgh.13729.
18. Wang YB, Zhang JY, Gong JP, Zhang F, Zhao Y. Balloon-occluded retrograde transvenous obliteration versus transjugular intrahepatic portosystemic shunt for treatment of gastric varices due to portal hypertension: a meta-analysis. J Gastroenterol Hepatol. 2016;31(4):727–33.
19. Saad WE, Kitanosono T, Koizumi J, Hirota S. The conventional balloon-occluded retrograde transvenous obliteration procedure: indications, contraindications, and technical applications. Tech Vasc Interv Radiol. 2013;16(2):101–51.
20. Kumamoto M, Toyonaga A, Inoue H, et al. Long-term results of balloon-occluded retrograde transvenous obliteration for gastric fundal varices: hepatic deterioration links to portosystemic shunt syndrome. J Gastroeterol Hepatol. 2010;25(6):1129–35.

Chapter 42
Interventional Radiology: Partial Splenic Embolization

Nobuhiko Taniai, Hiroshi Yoshida, and Eiigi Uchida

Abstract Partial splenic embolization (PSE) is an effective treatment for complications associated with hypersplenism and portal hypertension, such as esophagogastric varices, pancytopenia, portal hypertensive gastropathy, and ascites. PSE is indicated for all complications associated with hypersplenism and portal hypertension. PSE should not be indicated for patients with Child's C cirrhosis. A femoral artery approach is used for selective catheterization of the splenic artery. After an injection of antibiotics and steroids, embolization is achieved by injecting gelatin sponge cubes or coils. The most common complications after PSE are fever and left-sided abdominal pain, followed by retention of pleural effusion and ascites, splenic abscess, gastric ulcer, and others. There were no appreciable changes in the incidences of complications, but no patient had serious complications such as splenic abscess or portal vein thrombosis, which can frequently occur after splenectomy. PSE is a straightforward surgical technique associated with minimal complications and effectively improves hypersplenism and various complications associated with portal hypertension.

Keywords Partial splenic embolization (PSE) · Portal hypertension
Hypersplenism · Esophagogastric varices · Pancytopenia

N. Taniai (✉)
Department of Surgery,
Nippon Medical School Musashi Kosugi Hospital, Tokyo, Japan
e-mail: Taniain@nms.ac.jp

H. Yoshida · E. Uchida
Department of Surgery, Nippon Medical School Hospital, Tokyo, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_42

42.1 Introduction

Partial splenic embolization (PSE) is an effective treatment for complications associated with hypersplenism and portal hypertension, such as esophagogastric varices, pancytopenia, portal hypertensive gastropathy, and ascites. PSE also effectively suppresses elevated serum ammonia levels occurring after shunt embolization for hepatic encephalopathy [1–3]. Conventionally, splenectomy had been performed to improve hypersplenism and reduce portal vein pressure. Recently, new developments in interventional radiography have been made and rapidly disseminated in various fields, thereby facilitating minimally invasive treatment. PSE was first proposed by Maddison [4] in 1973, who used the technique to perform total splenic embolization in a patient with intractable esophageal variceal bleeding. Subsequently, many studies reported serious complications such as splenic abscess after PSE. In 1979, however, Spigos et al. [5] described a technique for partial embolization with antibiotic prophylaxis, which allowed PSE to be performed safely. Since then, PSE has been disseminated as a safe, reliable treatment [6].

Currently, PSE is performed in about ten hospitals not only for the treatment of portal hypertension but also for the improvement of pancytopenia associated with the treatment of hepatitis with interferon [7–14] and chemotherapy for hepatocellular carcinoma [15, 16], not only in Japan but also in Europe.

In this paper, we discuss the indications, techniques, complications, and therapeutic effectiveness of PSE.

42.2 Indications

PSE is indicated for all complications associated with hypersplenism and portal hypertension, such as esophagogastric varices, pancytopenia, portal hypertensive gastropathy, ascites, and shunt encephalopathy. The indications of PSE also include hematologic diseases, such as idiopathic thrombocytopenic purpura [17–22] and hereditary spherocytosis [23], as well as traumatic splenic injuries [24–36]. Because PSE can improve the bleeding tendency caused by factors such as thrombocytopenia [1, 37–41] and enhance liver function [1, 42, 43], it is not contraindicated in patients with a bleeding tendency or in patients with Child's C cirrhosis [1, 2].

42.3 Contraindications

PSE is contraindicated in patients who are sensitive to contrast media. The doses of contrast media should be minimized in patients in whom the use of general contrast media is contraindicated because of factors such as asthma and renal failure. While considering the patient's general condition, the embolic range can be adjusted, and additional treatment can be performed subsequently. Therefore, PSE can be performed in patients who are in poor general condition.

42.4 IVR Technique in Our Department

Celiac angiography is performed per the Seldinger method to confirm the route of the splenic arteries. Then a catheter is inserted into the splenic artery at the splenic hilum. Selective splenic angiography is performed to confirm the distribution of branches of the splenic arteries and the route of the splenic veins. An antibiotic and a steroid (hydrocortisone, 500 mg) are injected via the splenic artery. An antibiotic and gelatin sponge cubes suspended in contrast media (2–3 mm pieces) are injected as an embolic material via the splenic artery. The target embolic range is 70%. Whether the splenic veins are visualized must be confirmed (Fig. 42.1).

Recently, a microcatheter-based technique has been mainly used to selectively embolize branches of the splenic arteries (Figs. 42.2 and 42.3). This technique allows the splenic inferior artery to be selectively embolized [6]. Embolic materials regurgitated from the splenic artery can prevent embolism in the pancreatic magna, thereby precluding postoperative pancreatitis and pancreatic necrosis. Recently, coil embolization has been performed [44, 45] but is associated with several problems such as high cost and difficulty in performing repeated coil embolization.

If the collateral circulation can be visualized via the splenic artery, PSE should be performed after coil embolization of the collateral circulation to prevent complications (Fig. 42.4). After embolization, systemic administration of a steroid (hydrocortisone, 200 mg) and an antibiotic should be performed for 2 days, with 5-day use of suppositories containing nonsteroidal anti-inflammatory drugs, to prevent fever and left-sided abdominal pain. In patients with portal hypertension or esophagogastric varices, however, antiulcer agents and proton-pump inhibitors should be given to prevent peptic ulcer [46]. Before and 1 month after surgery, the embolic range should be confirmed on abdominal computed tomography (CT) (Fig. 42.5).

42.5 Complications

The most common complications after PSE are fever and left-sided abdominal pain, followed by retention of pleural effusion and ascites, splenic abscess, gastric ulcer, and others [47–49]. In our department, the following complications occurred soon after PSE: left-sided abdominal pain, 77.6%; fever, 94.8%; ascites retention, 5.2%; left pleural effusion, 3.4%; and splenic abscess, 1.7%. During the past 7 years, the incidences of complications in 76 patients were as follows: left-sided abdominal pain, 76.5%; fever, 91.2%; ascites retention, 8.8%; left pleural effusion, 5.9%; and splenic abscess, 0%. There were no appreciable changes in the incidences of complications, but no patient had serious complications such as splenic abscess or portal vein thrombosis which can frequently occur after splenectomy. However, two patients (1.5%) who died of sepsis caused by splenic abscess after 137 PSE procedures have been reported [47]. Therefore,

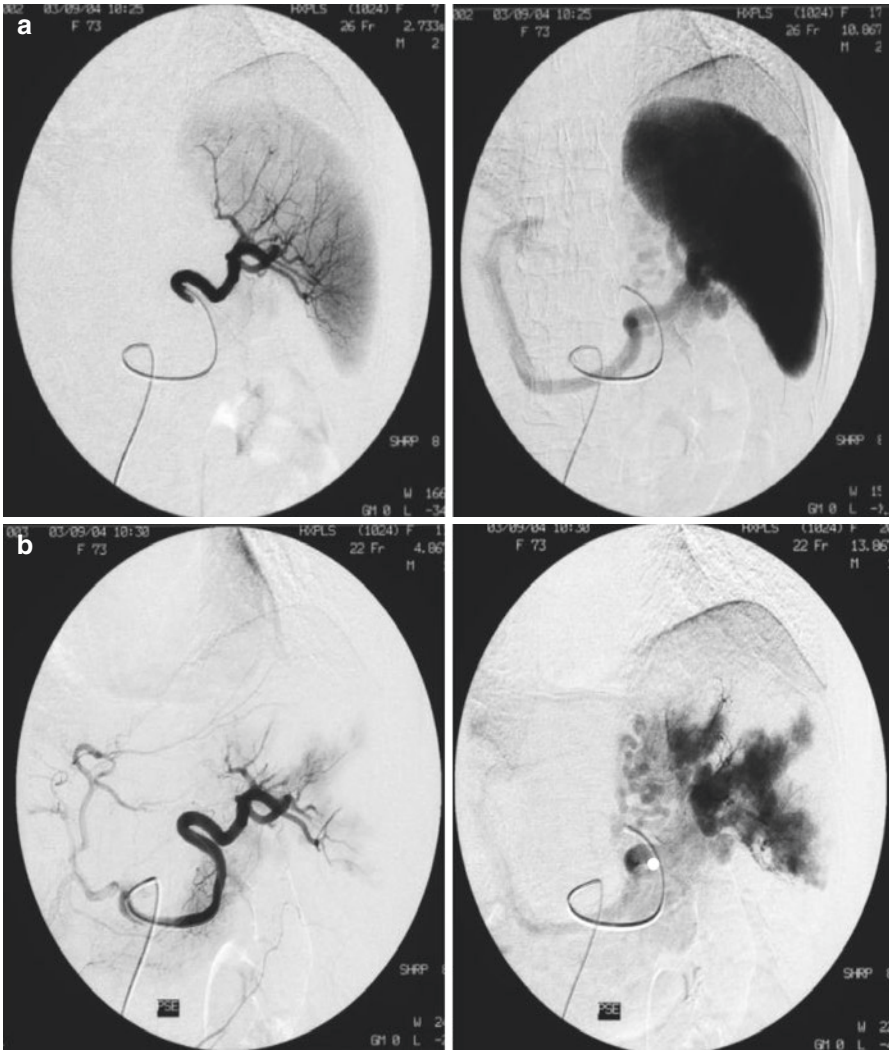


Fig. 42.1 (**a**) Arterial and venous phases during splenic angiography before PSE. (**b**) Arterial and venous phases during splenic angiography after PSE

the extent of embolism should be appropriately determined based on the pathological condition, such as massive ascites, portal vein thrombosis, and severe diabetes mellitus, of each patient. In addition, it is necessary to closely follow up patients and perform ultrasonography and CT and administer appropriate treatment as required.

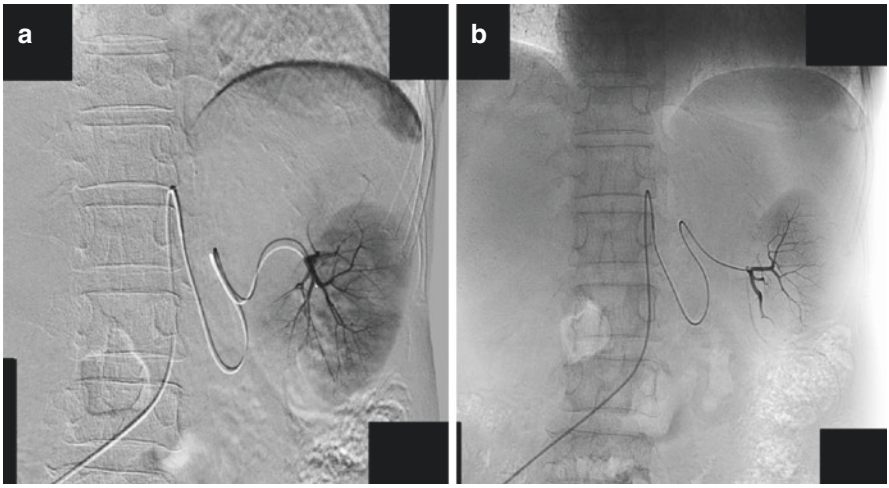


Fig. 42.2 (**a**) An angiographic image of the splenic inferior artery. (**b**) An angiographic image of the middle splenic artery

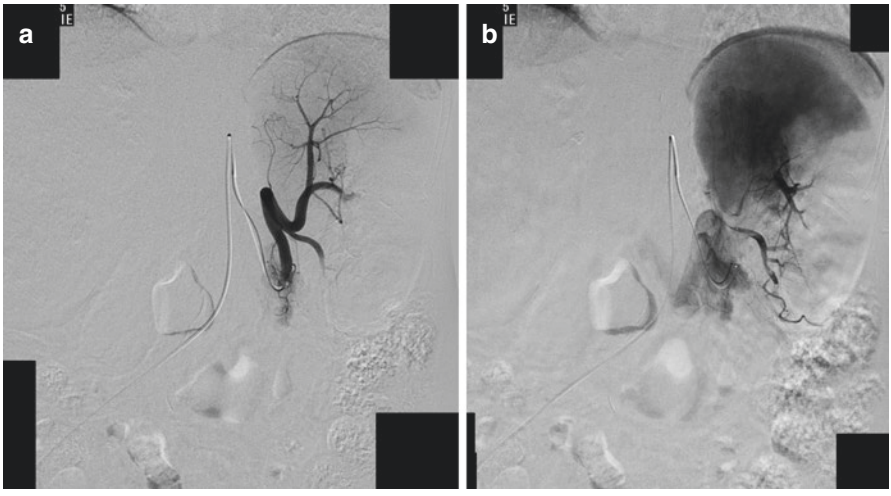


Fig. 42.3 (**a**) The arterial phase of an angiogram of the splenic artery after PSE. The middle and inferior splenic arteries were embolized, and only the inferior splenic branch was visualized. (**b**) The venous phase. The inferior splenic artery was embolized, and only the superior splenic artery was densely stained

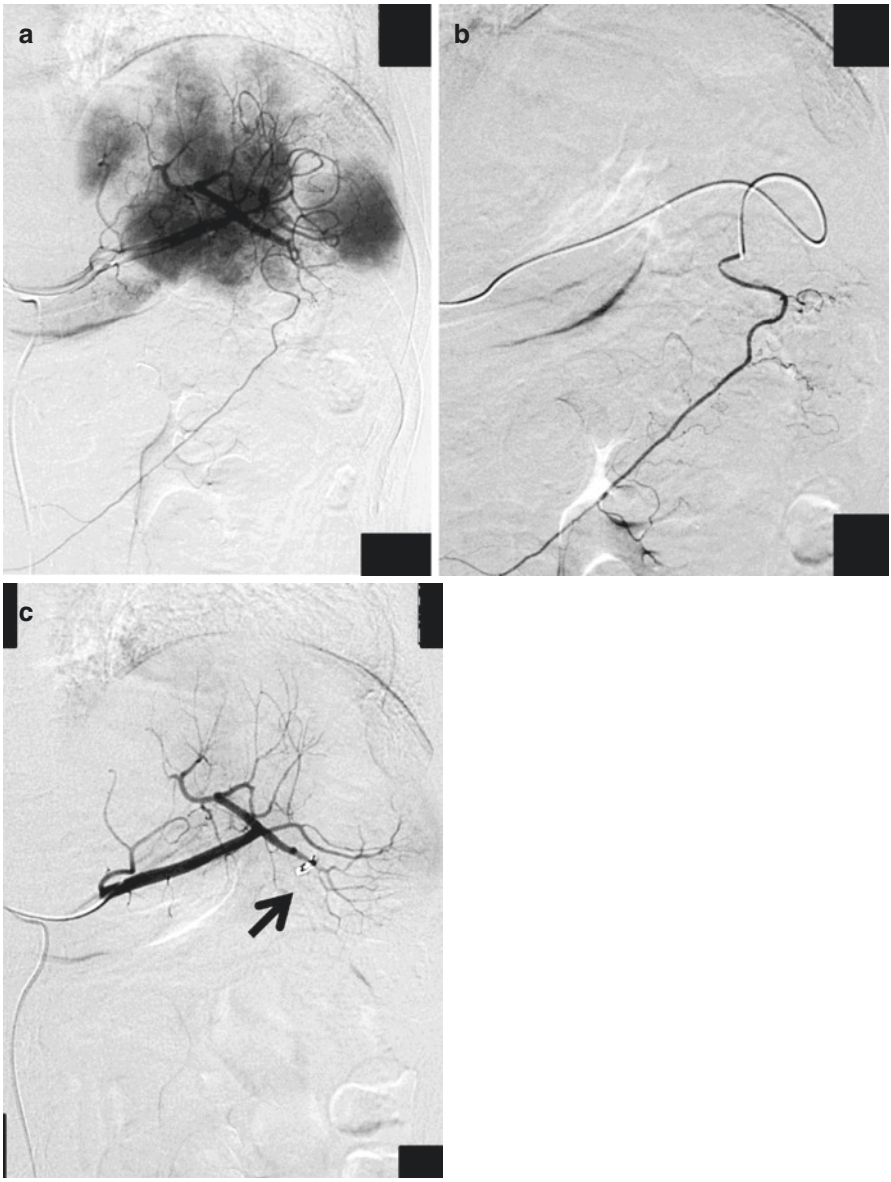


Fig. 42.4 (**a**) An splenic angiogram.The splenic artery contributed to the collateral circulation in the spleen and supplied blood to the retroperitoneum outside the spleen. (**b**) A microcatheter was inserted into the collateral circulation to perform coil embolization. (**c**) A splenic angiographic image, showing that no collateral circulation was visualized after embolization. The arrow shows the site of coil embolization

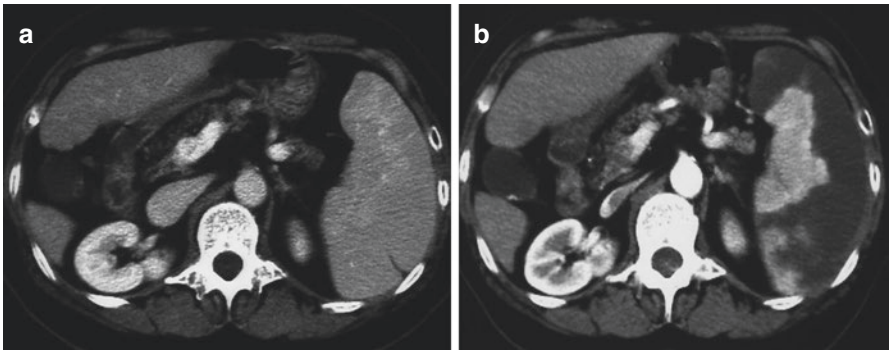


Fig. 42.5 (**a**) An abdominal contrast-enhanced computed tomographic scan obtained before PSE. (**b**) An abdominal contrast-enhanced computed tomographic scan obtained 1 month after PSE, showing that the spleen was extensively embolized

42.6 Treatment Outcomes

42.6.1 Pancytopenia

Platelet counts usually rise 12–24 h after PSE. The peak value is reached after about 2 weeks. The platelet count stabilizes after 2 months. The mean value is maintained at about twice the previous value for a prolonged time. Platelet counts increased from $8.2 \pm 3.9 \times 10^4/mm^3$ before PSE to a mean peak value of $16.9 \pm 6.9 \times 10^4/mm^3$ at 2 weeks after PSE and then gradually decreased. However, platelet counts remained significantly higher than pre-embolization values from 6 months, 2 years, 4 years, and 6 years to 8 years after PSE. (152%, 144%, 140%, 120%, and 150%, respectively) [1].

42.6.2 Esophagogastric Varices

The collateral blood flow is decreased, leading to an improvement in esophagogastric varices, prolongation of the treatment period for recurrence of esophagogastric varices, and an improvement in portal hypertensive gastropathy. Ohmagari et al. reported that PSE induced an 11% reduction in gastric mucosal hemoglobin content ($p < 0.01$), as assessed by reflectance spectrophotometry and significantly improved portal hypertensive gastropathy [50]. In particular, PSE combined with other procedures that can directly treat varices, such as endoscopic sclerotherapy and endoscopic variceal ligation (EVL), produces a significantly better outcome than a single procedure alone. Taniai et al. reported that the cumulative recurrence rates of

esophageal varices at 6 months, 1 year, and 2 years were significantly lower in patients undergoing PSE+EVL (21.1%, 37.0%, and 58.1%, respectively) than in those undergoing EVL alone (58.1%, 70.7%, and 80.4%, respectively). PSE is a supplemental treatment designed to prolong the effect of obliterating veins that feed and/or drain esophagogastric varices [2, 51].

42.6.3 Liver Function

Some studies have reported that PSE improves liver function for a prolonged time [1, 42, 43, 52–54]. Tajiri reported that cholinesterase activity and the serum albumin concentration increased significantly from 6 months after PSE and remained significantly elevated for many years. PSE can benefit patients with cirrhosis by improving hepatic protein synthesis [1]. Recently, Jiao reported that the levels of serum albumin were significantly increased and the levels of total bilirubin, international normalized ratio (INR), and globulin were sharply decreased at 6 months' post PSE. And Child-Pugh grade and ICG R15 at 6 m postoperatively were also improved significantly in PSE groups when compared with their preoperative state, as well as the values of the control group ($P < 0.05$) [54]. As for the mechanism, PSE can reduce portal venous pressure and destroy red blood cells, contributing to decreases in the prehepatic bilirubin burden and bilirubin levels. PSE can also reduce serum levels of factors that inhibit liver regeneration and thereby promote liver regeneration [52].

42.6.4 Living Donor Liver Transplantation

Splenic artery steal syndrome after liver transplantation causes ischemic biliary tract destruction or graft failure. PSE has been performed to improve blood flow in the hepatic arteries [37, 42, 43, 53, 54]. In patients in whom hypersplenism did not adequately resolve after transplantation, PSE should be additionally performed to improve hypersplenism. In our department, PSE has been performed before transplantation in patients with a platelet count of $5 \times 10^4/mm^3$ or less to increase platelet counts at the time of transplantation and to improve chronic hypersplenism after transplantation (unpublished data).

42.7 Conclusions

PSE is a straightforward IVR technique associated with minimal complications and effectively improves hypersplenism and various complications associated with portal hypertension.

References

1. Tajiri T, Onda M, Yoshida H, et al. Long-term hematological effects of partial splenic embolization in hepatic cirrhosis. Hepatogastroenterology. 2002;49:1445–8.
2. Taniai N, Onda M, Tajiri T, et al. Endoscopic variceal ligation (EVL) combined with partial splenic embolization (PSE). Hepatogastroenterology. 1999;46:2849–53.
3. Yoshida H, Mamada Y, Taniai N, et al. Long-term results of partial splenic artery embolization as supplemental treatment for hepatic encephalopathy associated with portal-systemic shunts. Am J Gastroenterol. 2005;100:43–7.
4. Maddison FE. Embolic therapy for hypersplenism. Intervest Radiol. 1973;8:280–1.
5. Spigos DG, Jonasson O, Mozes M, et al. Partial splenic embolization in the treatment of hypersplenism. AJR. 1979;132:777–82.
6. Yoshida H, Mamada Y, Taniai N, et al. Partial partial splenic embolization. Hepatol Res. 2008;28:225–33.
7. Ishikawa T, Abe S, Kojima Y, et al. Telaprevir-based triple therapy following partial splenic arterial embolization for chronic hepatitis C with thrombocytopenia can reduce carcinogenesis and improve hepatic function reserve. Exp Ther Med. 2015;10:1334–8.
8. Kondo C, Atsukawa M, Tsubota A, et al. Safety and efficacy of partial splenic embolization in telaprevir-based triple therapy for chronic hepatitis C. Intern Med. 2015;54:119–26.
9. Shimizu H, Takatsuka K, Nakano H, et al. Long-term evaluation of partial splenic embolization followed by interferon therapy in patient with hepatitis C virus (HCV) cirrhosis and thrombocytopenia. Inter Med. 2014;53:925–31.
10. Ikeda N, Imanishi H, Aizawa N, et al. Nationwide survey in Japan regarding splenectomy/partial splenic embolization for interferon treatment targeting hepatitis C virus-related chronic liver disease in patients with low platelet count. Hepatol Res. 2014;44:829–36.
11. Barcena R, Moreno A, Foruny JR, et al. Partial splenic embolization and peg-INF plus RBV in liver transplanted patients with hepatitis C recurrence; safety, efficacy and long-term outcome. Clin Transpl. 2010;24:366–74.
12. Miyake Y, Ando M, Kaji E, et al. Partial splenic embolization prior to combination therapy of interferon and ribavirin in chronic hepatitis C patients with thrombocytopenia. Hepatol Res. 2008;38:980–6.
13. Foruny FR, Blazquez J, Moreno A, et al. Safe use of pegylated interferon/ribavirin in hepatitis C virus cirrhotic patients with hypersplenism after partial splenic embolization. Eur J Gastroenterol Hepatol. 2005;17:157–64.
14. Moreno A, Barcena R, Blazqez J, et al. Partial splenic embolization for the treatment of hypersplenism in cirrhotic HIV/HCV patients prior to pegylated interferon and ribavirin. Antivir Ther. 2004;9:1027–30.
15. Huang JH, Gao F, Gu YK, et al. Combined treatment of hepatocellular carcinoma with partial splenic embolization and transcatheter hepatic arterial chemoembolization. World J Gastroenterol. 2007;13:6593–7.
16. Ooka Y, Chiba T, Ogasawara S, et al. Partial splenic embolization with transarterial chemoembolization in patients with hepatocellular carcinoma accompanied by thrombocytopenia. Biomed Res Int. 2014;2014:960628.
17. Portielje JE, Westendorp RG, Kluin-Nelemans HC, et al. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood. 2001;97:2549–54.
18. Schwartz J, Leber MD, Gillis S, et al. Long term follow-up after splenectomy performed for immune thrombocytopenic purpura (ITP). Am J Hematol. 2003;72:94–8.
19. Neylon AJ, Saunders PW, Howard MR, et al. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. Br J Haematol. 2003;122:966–74.
20. Uchida Y, Minoshima S, Miyazaki M, et al. Normalized spleen/liver ratios on 111In-labelled platelet scintigraphy to predict the outcome of partial splenic embolization in patients with idiopathic thrombocytopenic purpura. Nucl Med Commun. 2000;21:441–7.

21. Miyazaki M, Itoh H, Kaiho T, et al. Partial splenic embolization for the treatment of chronic idiopathic thrombocytopenic purpura. Am J Roentgenol. 1994;163:123–6.
22. Kimura F, Itoh H, Ambiru S, et al. Long-term results of initial and repeated partial splenic embolization for the treatment of chronic idiopathic thrombocytopenic purpura. Am J Roentgenol. 2002;179:1323–6.
23. Pratl B, Benesch M, Lackner H, et al. Partial splenic embolization in children with hereditary spherocytosis. Eur J Haematol. 2008;80:76–80.
24. Forsythe RM, Harbrecht BG, Peitzman AB. Blunt splenic trauma. Scand J Surg. 2006;95:146–51.
25. Rajani RR, Claridge JA, Yowler CJ, et al. Improved outcome of adult blunt splenic injury: a cohort analysis. Surgery. 2006;140:625–31.
26. Demetriades D, Hadjizacharia P, Constantinou C, et al. Selective nonoperative management of penetrating abdominal solid organ injuries. Ann Surg. 2006;244:620–8.
27. Smith HE, Biffl WL, Majercik SD, Jednacz J, Lambiase R, Cioffi WG. Splenic artery embolization: have we gone too far? J Trauma. 2006;61:541–4.
28. Stein DM, Scalea TM. Nonoperative management of spleen and liver injuries. J Intensive Care Med. 2006;21:296–304.
29. Gaarder C, Dormagen JB, Eken T, et al. Nonoperative management of splenic injuries: improved results with angioembolization. J Trauma. 2006;61:192–8.
30. Bessoud B, Denys A, Calmes JM, et al. Nonoperative management of traumatic splenic injuries: is there a role for proximal splenic artery embolization? Am J Roentgenol. 2006;186:779–85.
31. Cooney R, Ku J, Cherry R, et al. Limitations of splenic angioembolization in treating blunt splenic injury. J Trauma. 2005;59:926–32.
32. Rhodes CA, Dinan D, Jafri SZ, et al. Clinical outcome of active extravasation in splenic trauma. Emerg Radiol. 2005;11:348–52.
33. Ekeh AP, McCarthy MC, Woods RJ, et al. Complications arising from splenic embolization after blunt splenic trauma. Am J Surg. 2005;189:335–9.
34. Haan JM, Bochicchio GV, Kramer N, et al. Non-operative management of blunt splenic injury: a 5-year experience. J Trauma. 2005;58:492–8.
35. Hagiwara A, Fukushima H, Murata A, et al. Blunt splenic injury: usefulness of transcatheter arterial embolization in patients with a transient response to fluid resuscitation. Radiology. 2005;235:57–64.
36. Wahl WL, Ahrns KS, Chen S, et al. Blunt splenic injury: operation versus angio-graphic embolization. Surgery. 2004;136:891–9.
37. Firat A, Boyvat F, Moray G, et al. Comparison of two different percutaneous splenic artery interventions in the treatment of hypersplenism: preliminary report. Transplant Proc. 2005;37:1094–8.
38. Ohmoto K, Yamamoto S. Prevention of variceal recurrence, bleeding, and death in cirrhosis patients with hypersplenism, especially those with severe thrombocytopenia. Hepatogastroenterology. 2003;50:1766–9.
39. Nio M, Hayashi Y, Sano N, et al. Long-term efficacy of partial splenic embolization in children. J Pediatr Surg. 2003;38:1760–2.
40. Tajiri T, Onda M, Taniai N, et al. A comparison of combination endoscopic therapy and interventional radiology with esophageal transection for the treatment of esophageal varices. Hepatogastroenterology. 2002;49:1552–4.
41. Hidaka H, Kokubu S, Saigenji K, et al. Restoration of thrombopoietin production after partial splenic embolization leads to resolution of thrombocytopenia in liver cirrhosis. Hepatol Res. 2002;23:265–73.
42. Nussler NC, Settmacher U, Haase R, et al. Diagnosis and treatment of arterial steal syndromes in liver transplant recipients. Liver Transpl. 2003;9:596–602.
43. Uflacker R, Selby JB, Chavin K, et al. Transcatheter splenic artery occlusion for treatment of splenic artery steal syndrome after orthotopic liver transplantation. Cardiovasc Intervent Radiol. 2002;25:300–6.

44. Shimizu H, Takastuka K, Yoshida A, et al. Partial splenic embolization reverses insulin resistance in patients with liver cirrhosis. Intern Med. 2009;48:747–51.
45. Masada T, Tanaka T, Sakaguchi H, et al. Coils versus gelatin particles with or without intra-arterial antibiotics for partial splenic embolization: a comparative evaluation. J Vasc Interv Radiol. 2014;25:852–8.
46. Yoshida H, Mamada Y, Taniai N, et al. Interactions between anti-ulcer drugs and non-steroidal anti-inflammatory drugs in cirrhotic patients with bleeding esophagogastric varices. Hepatogastroenterology. 2009;56:1366–70.
47. Mozse MF, Spigos DG, Pollak R, et al. Partial splenic embolization, an alternative to splenectomy-results of a prospective, randomized study. Surgery. 1984;96:694–702.
48. Alwmark A, Bengmark S, Guulstrand P, et al. Evaluation of splenic embolization in patients with portal hypertension and hypersplenism. Ann Surg. 1982;96:518–24.
49. Sakai T, Shiraki K, Inoue H, et al. Complications of partial splenic embolization in cirrhotic patients. Dig Dis Sci. 2002;47:388–91.
50. Ohmagari K, Toyonaga A, Tanikawa K. Effects of transcatheter splenic arterial embolization on portal hypertensive gastric mucosa. Am J Gastroenterol. 1993;88:1837–41.
51. Tajiri T, Onda M, Taniai N, et al. A comparison of combination endoscopic therapy and interventional radiology with esophageal trisection for the treatment of esophageal varices. Hepatogastroenterology. 2002;49:1552–4.
52. Mukaiya M, Hirata K, Yamashiro K, et al. Changes in portal hemodynamics and hepatic function after partial splenic embolization (PSE) and percutaneous transhepatic obliteration (PTO). Cancer Chemother Pharmacol. 1994;33:37–41.
53. Barcena R, Moreno A, Foruny JR, et al. Improved graft function in liver-transplanted patients after partial splenic embolization: reversal of splenic artery steal syndrome? Clin Transpl. 2006;20:517–23.
54. Jiao S, Chen H, Wang Y, et al. Splenectomy versus partial splenic embolization for massive splenomegaly secondary to hepatitis B-related liver cirrhosis: a case- control study. Gastroenterol Res Pract. 2016;2016:3471626.

Chapter 43
Surgical Treatment: Sugiura Procedure and Hassab's Operation

Tsuyoshi Kurokawa, Takashi Arikawa, Tsuyoshi Sano, and Toshiaki Nonami

Abstract Non-shunt operations, such as the Sugiura procedure and Hassab's operation, consist of extensive interruption of collateral vessels connecting the high-pressure portal venous system in combination with splenectomy. Hemodynamic studies have suggested non-shunt operations do not divert portal blood flow, do not decompress the portal venous system, and maintain portal blood flow toward the liver. Among various kinds of non-shunt operations, the Sugiura procedure was the most effective because it was an extensive esophagogastric devascularization combined with esophageal transection and splenectomy. Its morbidity and mortality, however, were higher than those of other procedures. Accordingly, various authors have proposed modifications to make the procedure less complex. One common modification uses a single abdominal operation to achieve gastroesophageal devascularization. To achieve complete separation of the azygous vein system from the intramucosal vein and following anastomosis, an end-to-end anastomosing stapling device is used. Hassab's operation is also a single abdominal operation consisting of splenectomy and devascularization of the esophagus and the proximal part of the stomach. Different from the Sugiura procedure, it does not include esophageal transection. Recently, laparoscopic approaches have been increasingly indicated in various fields, including for patients with liver cirrhosis and portal hypertension. There have been some reports describing the techniques and outcomes of laparo-

T. Kurokawa (✉)
Department of Surgery, Masuko Memorial Hospital, Nagoya, Aichi, Japan

Meitetsu Hospital, Nagoya, Aichi, Japan
e-mail: t.kurokawa@meitetsu-hpt.jp

T. Arikawa · T. Sano
Department of Gastroenterological Surgery, Aichi Medical University, Nagakute, Aichi, Japan

T. Nonami
Department of Surgery, National Hospital Organization Higashi Nagoya National Hospital, Nagoya, Aichi, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_43

scopic non-shunt operations. Since 2008, we have completed 14 hand-assisted laparoscopic surgeries for Hassab's operation. In this chapter, we review the characteristics of each non-shunt operation and showed our latest results.

Keywords Sugiura procedure · Hassab's operation · Laparoscopic surgery

43.1 Introduction

Hemorrhage from esophagogastric varices is the major complication in patients with portal hypertension. Although most patients nowadays can be treated with endoscopic procedures or interventional radiology, some patients still need to be treated surgically with shunt operations or non-shunt operations. Because of the specific characteristics of shunt and non-shunt operations, it is difficult to evaluate which is appropriate for each patient. The choice of shunt or non-shunt is largely dependent upon patient's conditions and operator's skills. Reports have shown that surgeons tend to choose their favorite operations as optimal procedures at different medical units [1].

In view of the purpose of surgical treatment for portal hypertension, an appropriate procedure should have a low mortality, a low rate of rebleeding, a low incidence of hepatic coma, and less decompensation of hepatic function. Non-shunt operations, such as the Sugiura procedure and Hassab's operation described in this chapter, consist of extensive interruption of collateral vessels connecting the high-pressure portal venous system in combination of splenectomy. Hemodynamic studies have suggested non-shunt operations do not divert portal blood flow, do not decompress the portal venous system, and maintain or even slightly increase portal blood flow toward the liver [2]. Therefore, the incidence of hepatic coma is lower in patients receiving non-shunt operations than in those having portosystemic shunts [3].

43.2 Sugiura Procedure

Among non-shunt operations, the most effective strategy for preventing recurrent variceal hemorrhage is esophageal transection with paraesophagogastric devascularization and splenectomy, as advocated by Sugiura et al. [4]. The Sugiura procedure consists of both thoracic and abdominal operations. The thoracic procedure involves extensive paraesophageal devascularization up to the inferior pulmonary vein and esophageal transection. The abdominal procedure includes splenectomy, devascularization of the abdominal esophagus and cardia, and selective vagotomy and pyloroplasty (Fig. 43.1). As the Sugiura procedure may cause serious complications in high-risk patients, these two operations are often performed in two stages. According to their original report [4], the operative processes are summarized below.

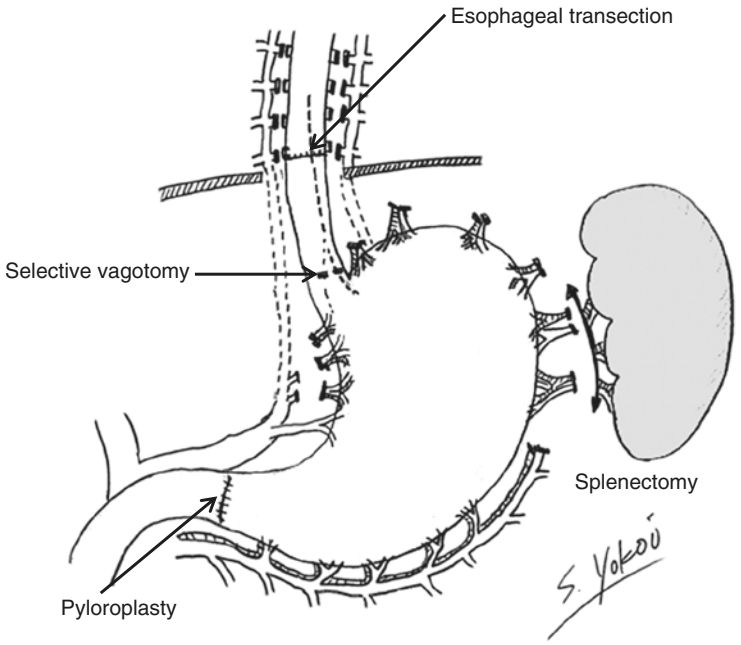


Fig. 43.1 Schematic representation of the Sugiura procedure

43.2.1 Thoracic Operation

A standard left lateral thoracotomy incision is made, entering beneath the sixth rib. Many dilated collateral veins resembling a vein plexus can be recognized around the esophagus. They are parallel to the vagus nerves and have many shunts to the esophagus. All of these shunting veins must be completely ligated and divided, with care taken not to damage the truncus vagalis and collateral veins. There are about 30–50 shunting veins to be ligated, and the length of devascularization of the thoracic esophagus is about 12–18 cm. Upon completion of devascularization, the esophagus is doubly clamped with forceps, and esophageal transection is performed at the level of the diaphragm. The anterior muscular layer and the mucosal layers of the esophagus are completely divided, with the posterior muscular layer left intact. The divided esophageal varices are not ligated in as much as ligation of the divided varices often causes postoperative stenosis. About 70–90 interrupted sutures are placed, and the divided varices are occluded with sutures. Then the muscle layer anastomosis is completed.

43.2.2 Abdominal Operation

Under an upper midline incision with left lateral extension, splenectomy is first performed. The abdominal esophagus and the cardia are devascularized from the greater curvature and the posterior of the stomach to the esophagus. The posterior gastric vagus nerve is divided by this procedure. Devascularization of the lesser curvature of the stomach and the abdominal esophagus follows, and the cardio-esophageal branches of the left gastric vessels are ligated and divided. The length of devascularization is about 7 cm, at the lesser curvature of the cardia. The esophagus and the cardia are completely mobilized and freed from the adjacent structures. Devascularization is facilitated by division of the anterior gastric vagus nerves. Pyloroplasty is necessary.

43.3 Modified Sugiura Procedure

Among the various kinds of non-shunt operations, the Sugiura procedure is the most effective because it is an extensive esophagogastric devascularization combined with esophageal transection and splenectomy. However, because of its complexity and high postoperative morbidity and mortality, this procedure has not been widely accepted especially in Western countries [5]. Accordingly, various authors have proposed modifications to make the procedure less complex [5, 6]. It showed not only low rates of rebleeding (4%) and hepatic coma (2.5%) but also no mortality and fewer postoperative complications [3]. It would be an effective and satisfactory operation for portal hypertension. One common modification uses a single abdominal operation to achieve gastroesophageal devascularization. A splenectomy is initially performed and is followed by usual devascularization. To achieve complete separation of the azygous vein system from the intramucosal vein and following anastomosis, an end-to-end anastomosing stapling device is used 3–5 cm above the gastroesophageal junction.

As described above, there are various modified Sugiura procedures nowadays; however, the original Sugiura procedure is considered to be maintaining its value in treating patients with extrahepatic portal vein thrombosis (PVT) and refractory variceal bleeding [7].

43.4 Hassab's Operation

Hassab's operation was reported before the Sugiura procedure by Hassab in 1967 [8]. It is a single abdominal operation and consists of splenectomy, devascularization of the esophagus and the proximal part of the stomach, vagotomy, and pyloroplasty. Different from the Sugiura procedure, it does not include esophageal

transection. Although lack of esophageal transection does not cause the gastric varices' regrowth, the recurrence rate of esophageal varices is higher compared with that in the Sugiura procedure [9]. This is the reason why Hassab's operation has been mainly indicated for the patients with gastric varices. However, the usefulness of endoscopic procedures has changed the therapeutic modality for gastroesophageal varices. Now Hassab's operation is considered to be a satisfactory approach to controlling varices resistant to or recurrent after endoscopic therapy when combined with preoperative endoscopic procedures [10]. Furthermore, other characteristics of Hassab's operation include beneficial changes in the hepatic hemodynamic status and effect of splenectomy on liver regeneration as well as the canceling of pancytopenia [10–12].

43.4.1 Laparoscopic Hassab's Operation

Owing to the cumulative experiences of laparoscopic surgeries and recent advances in operating devices, especially vessel-sealing systems, laparoscopic approaches have been increasingly indicated in various fields, including for patients with liver cirrhosis and portal hypertension [13, 14]. In 2008, we revised the past operative method and have chosen a hand-assisted laparoscopic surgery (HALS) for Hassab's operation in patients with portal hypertension. We experienced HALS for 14 Hassab's operations up to the present. Indications for this operation should be completely the same as for the open method. In our series, all patients were treated combined with perioperative endoscopic procedures. The perioperative data for each patient are shown in Tables 43.1 and 43.2. There is no patient who was converted to the open method. The operative time ranged from 194 to 547 min (342 ± 90 min) with intraoperative blood loss ranging from 24 to 1131 g (460 ± 385 g). Two patients required red cell concentrate (RCC) transfusion. As complications, massive ascites occurred in two patients. In eight patients, portal vein thrombus developed.

43.4.2 Operative Procedure

We have reported our operative details [15]. Patients are placed in a semilateral position with the left flank elevated at a 45° angle. While dissecting the splenogastric ligaments and the splenic hilar pedicle, the operation bed is rotated to render the patient's position horizontal. Three 12-mm laparoscope trocars are inserted, and a 7–7.5-cm midline incision is made for hand as shown Fig. 43.2. A purely laparoscopic method was used until the completion of splenic mobilization unless bleeding occurred. Splenic attachments are divided using a vessel-sealing system. After the upper pole of the spleen is entirely dissected away from the diaphragm, we transect the splenic hilar pedicles with an endoscopic linear vascular stapler. HALS is introduced from dissection of splenic hilar pedicles. Then we start

Table 43.1 The perioperative data for each patient (1)

No	Age	Gender	Ethiology	Spleen volume (mL)	Plt $\times 10^4/\mu L$	Operative method	Concomitant procedures	Conversion
1	73	M	C-LC, EV+GV	790	4.4	L-Has (HALS)	Non	No
2	65	M	Alcohol, EV+GV	575	11.2	L-Has (HALS)	Non	No
3	72	M	PBC, EV+GV	755	2.0	L-Has (HALS)	Wedge biopsy of liver	No
4	63	M	C-LC, EV	870	4.8	L-Has (HALS)	Non	No
5	65	M	Alcohol, EV+GV	320	10.2	L-Has (HALS)	Non	No
6	37	M	Alcohol, EV+GV	525	11.7	L-Has (HALS)	Non	No
7	60	F	B-LC, EV	630	3.0	L-Has (HALS)	Non	No
8	79	M	C-LC, EV, HCC (S8)	697	4.8	L-Has (HALS)	Radiofrequency ablation	No
9	67	M	B-LC, EV, Post-Hx	1265	4.5	L-Has (HALS)	Non	No
10	63	M	B-LC, EV, Post-Hx, HCC (S3, S8)	Not estimated	7.1	L-Has (HALS)	Partial liver resectioon×2	No
11	66	M	C-LC, EV+GV	486	8.3	L-Has (HALS)	Non	No
12	67	F	NASH, EV+GV	830	8.2	L-Has (HALS)	Wedge biopsy of liver	No
13	53	M	NASH, EV+GV	1090	3.5	L-Has (HALS)	Wedge biopsy of liver	No
14	66	M	C-LC, EV	645	5.5	L-Has (HALS)	Non	No

Abbreviations: *C-LC* liver cirrhosis (type C), *EV* esophageal varices, *GV* gastric varices, *PBC* primary biliary cirrhosis, *HCC* hepatocellular carcinoma, *B-LC* liver cirrhosis (type B), *Hx* hepatectomy, *NASH* non-alcoholic steatohepatitis, *L-Has* laparoscopic Hassab's procedure, *HALS* hand-assisted laparoscopic surgery

devascularization of the upper stomach and abdominal esophagus. Devascularization is performed in an inferior-to-superior direction, starting at the middle of the greater curvature of the stomach with the vessel-sealing system. The gastrohepatic ligament is then opened, and devascularization of the lesser curvature is performed by the same method. In patients with gastric varices, a large draining vein is seen in the area of the upper gastric fundus. This vessel is ligated with a 3-0 absorbable thread. After isolation of the anterior and posterior vagus nerves with the surgeon's fingers, nerves and vessels are dissected superior to a point about 7 cm from the esophagocardia junction (Fig. 43.3).

Table 43.2 The perioperative data for each patient (2)

Case	Blood loss (g)	Blood transfusion RCC	FFP	PC	Operative time (min)	SSI	Complications	POS (days)
1	692	0	0	10U	397	No	Massive ascites, PVT	21
2	1065	4U	0	0	458	No	Non	8
3	680	0	0	10U	383	No	PVT	41
4	122	0	0	20U	194	No	Non	18
5	24	0	0	0	278	No	PVT	21
6	600	0	0	0	337	No	PVT	19
7	925	0	0	10U	322	No	Non	13
8	1131	0	0	10U	280	No	Non	18
9	97	0	0	10U	413	No	PVT	27
10	353	0	0	15U	547	No	PVT	20
11	118	0	0	0	302	No	PVT	15
12	156	0	0	0	303	Yes	Massive ascites, PVT	28
13	347	0	0	10U	275	No	Non	11
14	135	0	0	10U	303	No	Gastric stasis	27

Abbreviations: *RCC* red cell concentrates, *FFP* fresh frozen plasma, *PC* platelet concentrates, *SSI* surgical site infection, *PVT* portal vein thrombus, *POS* post-operative hospital stay

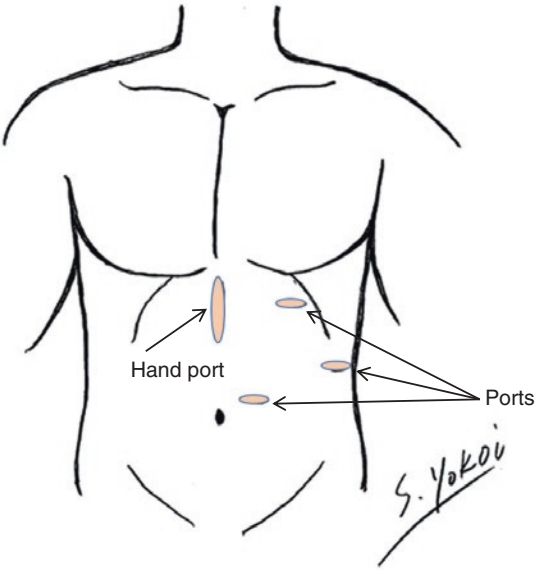


Fig. 43.2 Port sites in our laparoscopic Hassab's operation

43.5 Complications Associated with Splenectomy

Although splenectomy is growing in importance for patients with liver cirrhosis and portal hypertension, the indications for splenectomy remain controversial because of portal vein thrombosis (PVT) and septic complications. Recently, it has been

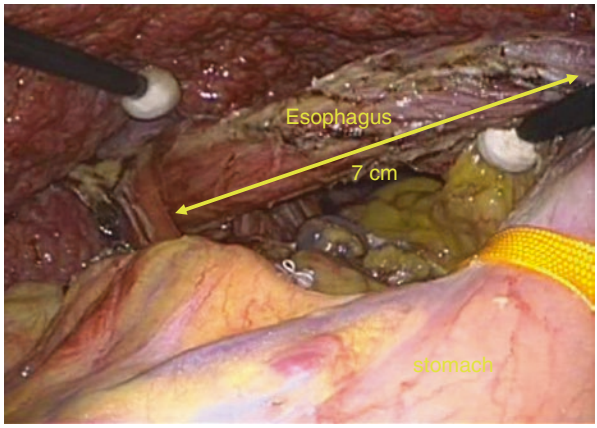


Fig. 43.3 Devascularization of the esophagus in our laparoscopic Hassab's operation

reported that PVT is not a rare complication of splenectomy [16, 17]. In our series, major postoperative complications included ascites and PVT. PVT causes the liver dysfunction after operation. Due attention should be paid to it and quick measures must be undertaken.

Furthermore, postsplenectomy septic complications may be lethal. Pneumococcal vaccination before operation is crucial, and elderly patients or those with low immune function should not be operated; indications should be strictly followed.

References

1. Yang CM. Portal hypertension. In: Hua JD, editor. Modern general surgery. 1st ed. Beijing: People's Military Medical Publisher; 1999. p. 949.
2. Wang Y. Surgical treatment of portal hypertension. Hepatobiliary Pancreat Dis Int. 2002;1:211–4.
3. Ma YG, Li XS, Zhao J, et al. Modified Sugiura procedure for the management of 160 cirrhotic patients with portal hypertension. Hepatobiliary Pancreat Dis Int. 2004;3:399–401.
4. Sugiura M, Futagawa S. A new technique for treating esophageal varices. J Thoracic Cardiovascular Surg. 1973;66:677–84.
5. Selzner M, Tuttle-Newhall JE, Dahm F, et al. Current indication of a modified Sugiura procedure in the management of variceal bleeding. J Am Coll Surg. 2001;193:166–73.
6. Soonawalla ZF, Shah SR, Mathur SK. Modified Sugiura procedure. J Am Coll Surg. 2002;194:247.
7. Cheng EY, Zarrinpar A, Geller DA, Goss JA, Busutil RW. Liver: nonshunt surgical management of refractory variceal bleeding. In: Brunicardi FC, Anderson DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE, editors. Schwartz's principles of surgery. 10th ed. New York: McGraw-Hill Education; 2015. p. 1283.
8. Hassab MA. Gastroesophageal decongestion and splenectomy in the treatment of esophageal varices in bilharzial cirrhosis: further studies with a report on 355 operations. Surgery. 1967;61:169–76.

9. Zhan Y, Wen T, Yan L, et al. The changes of hepatic hemodynamics and functional hepatic reserve after splenectomy with periesophagogastric devascularization. Hepatogastroenterology. 2009;56:835–9.
10. Hayashi H, Takamura H, Yamaguchi Y, et al. Recent role of Hassab's operation for cirrhotic patients: combination with endoscopic procedure for varices. Asian J Surg. 2012;35:57–61. https://doi.org/10.1016/j.asjsur.2012.04.024.
11. Murata K, Shiraki K, Sugimoto K, et al. Splenectomy enhances liver regeneration through tumor necrosis factor (TNF)-alpha following dimethylnitrosamine-induced cirrhotic rat model. Hepatogastroenterology. 2001;48:1022–7.
12. Ueda S, Yamanoi A, Hirakawa Y, et al. Transforming growth factor-beta1 released from the spleen exerts a growth inhibitory effect on liver regeneration in rats. Lab Investig. 2003;83:1593–603.
13. Nicholson IA, Falk GL, Mulligan SC. Laparoscopically assisted massive splenectomy. A preliminary report of the technique of early hilar devascularization. Surg Endosc. 1998;12:73–5.
14. Wang Y, Zhan X, Zhu Y, et al. Laparoscopic splenectomy in portal hypertension: a single-surgeon 13-year experience. Surg Endosc. 2009;24:1164–9. https://doi.org/10.1007/s00464-009-0744-4.
15. Ando K, Kurokawa T, Nagata H, et al. Laparoscopic surgery in the management of hypersplenism and esophagogastric varices: our initial experiences. Surg Innov. 2012;19(4):421–7. https://doi.org/10.1177/1553350611432724.
16. Winslow ER, Brunt LM, Drebin JA, et al. Portal vein thrombosis after splenectomy. Am J Surg. 2002;184:631–6.
17. Kinjo N, Kawanaka T, Akahoshi T, et al. Risk factors for portal venous thrombosis after splenectomy in patients with cirrhosis and portal hypertension. Br J Surg. 2010;97:910–6.

Chapter 44
Surgical Treatment: Selective Shunt Surgery

Hiroshi Yoshida, Hiroshi Makino, Tadashi Yokoyama, Hiroshi Maruyama, Atsushi Hirakata, Junji Ueda, Hideyuki Takata, Yasuhiro Mamada, Nobuhiko Taniai, and Eiji Uchida

Abstract A number of surgical procedures have been developed for the management of esophagogastric varices. They can be broadry classified into shunting and nonshunting procedures. There are two types of shunting procedure, namely nonselective and selective. Nonselective shunts, such as portacaval or mesocaval shunts, effectively reduce the incidence of variceal bleeding, but they carry a high risk of postoperative encephalopathy as a result of hyperammonemia. Selective shunts such as the distal splenorenal shunt (DSRS) or left gastric venous caval shunt were developed to preserve portal blood flow through the liver and reduce esophagogastric variceal pressure. The DSRS effectively prevents rebleeding, but it still carries a risk of postoperative encephalopathy. In order to prevent both postoperative encephalopathy and bleeding, we have improved the DSRS procedure by additionally performing splenopancreatic disconnection and gastric transection.
In conclusion, endoscopic treatments have been developed recently and are performed widely performed for esophagogastric varices; however, surgery in the form of DSRS is also useful for managing esophagogastric varices in patients with idiopathic portal hypertension in the absence of severe liver pathologies.

Keywords Distal splenorenal shunt · Esophagogastric varices · Portal hypertension · Selective shunt

H. Yoshida (✉) · Y. Mamada · E. Uchida
Department of Surgery, Nippon Medical School, Tokyo, Japan
e-mail: hiroshiy@nms.ac.jp

H. Makino · T. Yokoyama · H. Maruyama · A. Hirakata · J. Ueda · H. Takata
Department of Surgery, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan

N. Taniai
Department of Surgery, Nippon Medical School Musashi Kosugi Hospital, Tokyo, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_44

44.1 Introduction

There are a variety of treatments for esophagogastric varices, including endoscopic treatment, interventional radiology, and surgery [1–3]. Although the recurrence rate after surgery is low, because of the invasive nature of surgery, it is usually reserved for refractory cases. A number of surgical procedures have been developed to manage esophagogastric varices [4]; and they can be classified into two: shunting and nonshunting procedures.

44.2 Various Shunting Procedures

Various shunting procedures have been developed for treating esophagogastric varices [5–23] (Table 44.1). The goal of shunting is to prevent the incidence of variceal bleeding by reducing variceal pressure. There are two types of shunting procedures, namely nonselective and selective. Portacaval, mesocaval, mesorenal, and proximal splenorenal shunts are nonselective. Nonselective shunts reduce both portal venous and variceal pressure. The distal splenorenal shunt (DSRS) and left gastric venous caval shunt (Inokuchi shunt) are selective. Selective shunts maintain portal pressure but selectively reduce esophagogastric variceal pressure. Nonselective shunts are good for preventing recurrent bleeding. Mesocaval shunt is one of the popular techniques for elective or emergency control of variceal hemorrhage. However, nonselective shunts carry a high risk of postoperative encephalopathy as a result of hyperammonemia [24–26]. Patients with hyperammonemia require long-term nutritional support, and this can have a negative effect on their quality of life. Even with selective shunts, loss of shunt selectivity, and consequent postoperative encephalopathy, can occasionally occur [6, 12].

Table 44.1 Shunt procedures used to treat esophagogastric varices

Shunting procedure
Nonselective shunt
Portocaval shunt
Mesocaval shunt
Mesorenal shunt
Proximal splenorenal shunt
Selective shunt
Distal splenorenal shunt (DSRS)
Left gastric venacaval shunt (Inokuchi shunt)

44.3 Selective Shunts

44.3.1 Left Gastric Venous Caval Shunt (Inokuchi Shunt)

44.3.1.1 Surgical Procedure

To maintain postoperative portal perfusion and prevent postoperative encephalopathy, in 1967 Inokuchi designed a selective shunt called the left gastric venous caval shunt [5, 17, 21–23].

This shunt procedure consists of anastomosis of the distal end of the transected left gastric vein to the inferior vena cava, together with splenectomy. An autograft from the great saphenous vein is anastomosed to the inferior vena cava in an end-to-side fashion, and the opposite end is pulled through the suprapancreatic space. After the anastomosis is completed, splenectomy is performed.

44.3.1.2 Clinical Results

The operative mortality rates are satisfactorily low at 2.8% overall and 3.7% in the cirrhotic cases after an average follow-up period of 9 years and 7 months. Bleeding after surgery was found in only 8.0% of all patients and 7.9% in cases with liver cirrhosis. The diameter of the portal vein was marginally changed from the preoperative mean of 15.9 mm to 13.2 mm at the end of the period. The portal flow was well maintained at the mean of 680 mL/min at a remote follow-up.

44.3.2 DSRS

44.3.2.1 Original DSRS (Fig. 44.1)

The DSRS is a selective shunt that was developed by Warren in its original form in 1967 [10] to assure postoperative hepatofugal flow through the liver and transsplenic variceal decompression. The spleen can be preserved in this procedure; therefore, it is commonly chosen for use in young patients with esophagogastric varices.

The procedure consists of anastomosis of the distal end of the splenic vein to the left renal vein and devascularization of the left gastric artery and vein. The pancreas is approached via the lesser sac. After dissection of the distal part of the splenic vein from the pancreas, it is important to make sure that the vein is pulled down to the left renal vein without being kinked: the anastomosis needs to be performed without tension or kinking of this vein. Continuous sutures are used to place the anastomosis

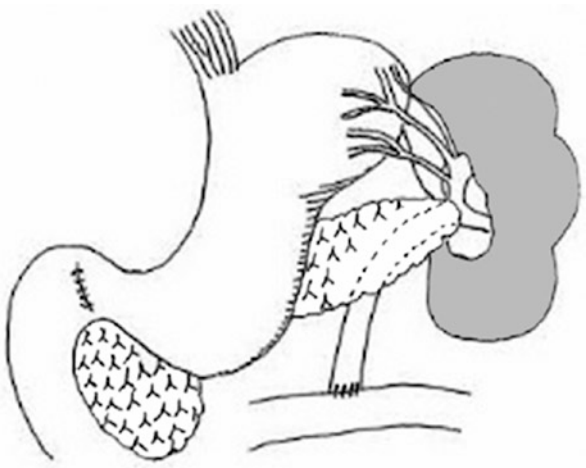


Fig. 44.1 Original DSRS

on the left renal vein just in front of the ligated adrenal vein. The coronary venous system is disconnected from the portal system by devascularization of the left gastric artery and vein.

The specific objectives of DSRS, as stated in the original publication [10], were (1) selective reduction of blood flow pressure and volume through gastroesophageal veins, (2) maintenance of portal venous perfusion of the liver, and (3) maintenance of continuous venous hypertension in the intestinal vascular bed. These three objectives have formed the basis for many subsequent researches.

Stenosis due to DSRS can lead to elevation of variceal pressure, accompanied by the risk of rebleeding. Shunt stenosis can be managed by balloon dilation [27]. DSRS effectively prevents rebleeding, but it still carries a risk of hyperammonemia [12]. Loss of shunt selectivity via the pancreatic vein during long-term follow-up has been confirmed in patients who have undergone the original DSRS procedure [6].

44.3.2.2 DSRS with Splenopancreatic Disconnection (SPD)

To avoid loss of shunt selectivity via the pancreatic vein, Warren et al. [28] subsequently improved the DSRS procedure by adding splenopancreatic disconnection (SPD)—in other words, skeletonization of the splenic vein from the pancreas to its bifurcation at the splenic hilum. The whole pancreas is mobilized along its inferior border from the superior mesenteric vein to the splenic hilus, and the pancreatic perforating veins are ligated as they enter the splenic vein. However, with SPD, loss of shunt selectivity via collateral pathways through the stomach has still been observed [18] (Fig. 44.2).

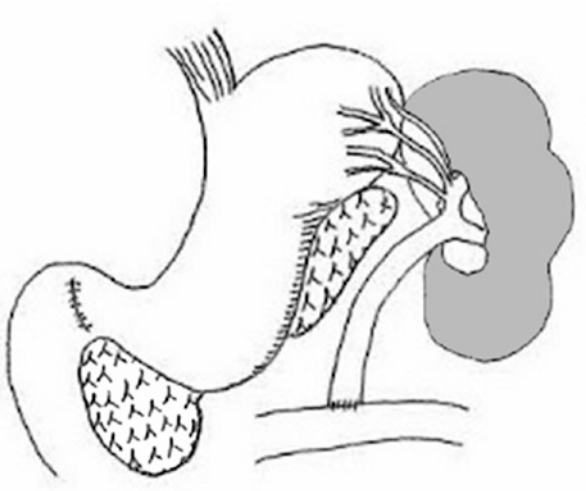


Fig. 44.2 DSRS with SPD

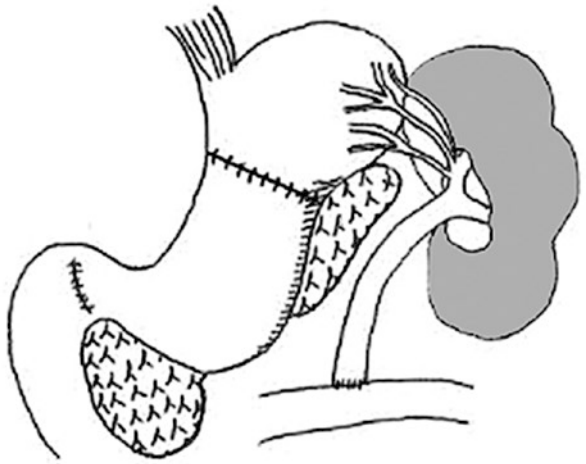


Fig. 44.3 DSRS with SPD plus GT

44.3.2.3 DSRS with SPD Plus Gastric Transection (GT)

We modified DSRS by additionally performing both SPD and gastric transection (GT) to prevent loss of shunt selectivity. Katoh et al. [29] transected and resutured the seromuscular layer of the upper stomach to prevent loss of selectivity after DSRS with SPD. They called this procedure "superselective DSRS." However, whereas Katoh et al. transected only the seromuscular layer of the upper stomach, we transected all layers of the upper stomach. GT involved transection and anastomosis of the upper stomach with an autosuture instrument; the short gastric arteries and veins were spared (Fig. 44.3).

44.3.2.4 Clinical Data on DSRS

Previously, we compared the long-term outcomes in cirrhotic patients who underwent DSRS with those in patients who underwent esophageal transection (i.e., a nonshunting procedure) as a treatment for esophageal varices. No recurrent varices were observed in the DSRS group. The cumulative recurrence rate of varices in the esophageal transection group was 31.6% at 5 years and 52.5% at 10 years. The cumulative rates of hyperammonemia at 5 and 10 years were significantly higher in the DSRS group (30.4% and 30.4%, respectively) than in the esophageal transection group (0% and 5.6%) ($P < 0.01$). Cumulative survival rates in the DSRS group vs. the esophageal transection group did not differ significantly, at 90.9% vs. 94.7% at 5 years and 85.2% vs. 81.7% at 10 years. These results suggest that DSRS is more effective than esophageal transection in preventing recurrence of esophageal varices, but that it is associated with a higher incidence of hyperammonemia [19].

We compared the long-term results of three types of DSRS (original DSRS, DSRS with SPD, DSRS with SPD plus GT) in treating esophageal varices. No significant differences were observed in survival among the three groups. The prevalence of hyperammonemia in the DSRS with SPD plus GT group (0% at 1 year, 9.1% at 5 years, and 9.1% at 10 years) was significantly lower than that in the original DSRS group or the DSRS with SPD group ($P < 0.01$). Loss of shunt selectivity promotes hyperammonemia and decreases portal blood flow. DSRS with SPD plus GT may reduce the incidence of postoperative hyperammonemia [12].

In a randomized controlled trial, Galambos et al. [30] compared nonselective shunts with selective shunts for treating bleeding esophageal varices. Mortality rates, frequencies of shunt occlusion, and frequencies of recurrent gastrointestinal bleeding were similar. Encephalopathy developed significantly more commonly after nonselective shunt placement than after selective shunt placement. Deterioration of hepatic function was significantly greater after placement of a nonselective shunt than after selective shunt placement.

In a prospective, randomized trial, Rikkers et al. [11] evaluated the effectiveness of DSRS. At the first postoperative evaluation, quantitative measures of hepatic function were similar to the preoperative values after the selective shunt procedure, but they were significantly lower after nonselective shunt placement. Early postoperative angiography revealed the preservation of hepatic portal perfusion in 14 of 16 selective shunt patients (88%) but in only 1 of 20 nonselective shunt patients ($P < 0.001$). Encephalopathy did not develop in any patient with continued portal perfusion, as compared with 45% of patients without portal flow ($P < 0.05$). Overall, postoperative encephalopathy developed in significantly fewer patients who received selective shunting (selective, 12%; nonselective, 52%; $P < 0.001$). Rikkers et al. concluded that the DSRS especially when its objective of maintaining hepatic portal perfusion was achieved resulted in significantly less morbidity than nonselective shunting.

Warren et al. [31] reported the metabolic basis of portosystemic encephalopathy and compared the effects of selective vs. nonselective shunts. The maximum rate of urea synthesis did not change in patients with DSRS, but it decreased significantly in those with nonselective shunts.

We also evaluated the results of shunting and nonshunting procedures for the treatment of esophagogastric varices in patients with idiopathic portal hypertension (IPH). Patients were allocated to two groups: a shunting group (four who underwent DSRS) and a nonshunting group (three who underwent esophageal transection and two who underwent the Hassab procedure). No recurrence was observed in the shunting group. In the nonshunting group, esophagogastric varices recurred in all four patients whose varices had been completely eradicated. The postsurgical increase in the platelet count was observed at significantly fewer times in the shunting group (1.7 ± 0.2 times) than in the nonshunting group (5.8 ± 2.9 times) ($P = 0.0267$). Portal venous thrombosis did not develop in the shunting group, but it appeared in four patients (80.0%) in the nonshunting group. No patient developed loss of shunt selectivity or portal-systemic encephalopathy. DSRS was thus useful for the management of esophagogastric varices in patients with IPH [32].

44.4 Conclusion

Endoscopic treatments for esophagogastric varices have recently been developed and widely accepted as a first-line treatment, but DSRS is also useful for managing esophagogastric varices in patients with IPH in the absence of severe liver pathologies.

References

1. Yoshida H, Mamada Y, Taniai N, Tajiri T. New methods for the management of esophageal varices. World J Gastroenterol. 2007;13:1641–5.
2. Yoshida H, Mamada Y, Taniai N, Tajiri T. New methods for the management of gastric varices. World J Gastroenterol. 2006;12:5926–31.
3. Yoshida H, Mamada Y, Taniai N, et al. Treatment modalities for bleeding esophagogastric varices. J Nippon Med Sch. 2012;79:19–30.
4. Yoshida H, Mamada Y, Taniai N, Tajiri T. New trends in surgical treatment for portal hypertension. Hepatol Res. 2009;39:1044–51.
5. Inokuchi K, Kobayashi M, Kusaba A, Ogawa Y, Saku M, Shiizaki T. New selective decompression of esophageal varices. By a left gastric venous-caval shunt. Arch Surg. 1970;100:157–62.
6. Belghiti J, Grenier P, Nouel O, Nahum H, Fekete F. Long-term loss of Warren's shunt selectivity. Angiographic demonstration. Arch Surg. 1981;116:1121–4.
7. Shields R. Small-diameter PTFE portosystemic shunts: portocaval vs mesocaval. HPB Surg. 1998;10:413–4.
8. Mercado MA, Morales-Linares JC, Granados-Garcia J, Gomez-Mendez TJ, Chan C, Orozco H. Distal splenorenal shunt versus 10-mm low-diameter mesocaval shunt for variceal hemorrhage. Am J Surg. 1996;171:591–5.
9. Paquet KJ, Lazar A, Koussouris P, et al. Mesocaval interposition shunt with small-diameter polytetrafluoroethylene grafts in sclerotherapy failure. Br J Surg. 1995;82:199–203.
10. Warren WD, Zeppa R, Fomon JJ. Selective trans-splenic decompression of gastroesophageal varices by distal splenorenal shunt. Ann Surg. 1967;166:437–55.

11. Rikkers LF, Rudman D, Galambos JT, et al. A randomized, controlled trial of the distal splenorenal shunt. Ann Surg. 1978;188:271–82.
12. Tajiri T, Onda M, Yoshida H, et al. Long-term results of modified distal splenorenal shunts for the treatment of esophageal varices. Hepatogastroenterology. 2000;47:720–3.
13. Stipa S, Balducci G, Ziparo V, Stipa F, Lucandri G. Total shunting and elective management of variceal bleeding. World J Surg. 1994;18:200–4.
14. Klein AS, Fair JH, Cameron JL. Suprarenal mesocaval shunt. Surg Gynecol Obstet. 1991;173:319–22.
15. Sato Y, Hatakeyama K. Left gastric venous caval direct shunt in esophagogastric varices. Hepatogastroenterology. 2002;49:1251–2.
16. Inokuchi K, Beppu K, Koyanagi N, Nagamine K, Hashizume M, Sugimachi K. Exclusion of nonisolated splenic vein in distal splenorenal shunt for prevention of portal malcirculation. Ann Surg. 1984;200:711–7.
17. Inokuchi K. Selective decompression of esophageal varices by a left gastric venacaval shunt. Surg Annu. 1978;10:215–36.
18. Henderson JM, Warren WD, Millikan WJ, Galloway JR, Kawasaki S, Kutner MH. Distal splenorenal shunt with splenopancreatic disconnection. A 4-year assessment. Ann Surg. 1989;210:332–9; discussion 9–41.
19. Tajiri T, Onda M, Yoshida H, Mamada Y, Taniai N, Yamashita K. Comparison of the long-term results of distal splenorenal shunt and esophageal transection for the treatment of esophageal varices. Hepatogastroenterology. 2000;47:1619–21.
20. Rikkers LF. Definitive therapy for variceal bleeding: a personal view. Am J Surg. 1990;160:80–5.
21. Inokuchi K, Beppu K, Koyanagi N, et al. Fifteen years' experience with left gastric venous caval shunt for esophageal varices. World J Surg. 1984;8:716–21.
22. Inokuchi K, Kobayashi M, Ogawa Y, Saku M, Nagasue N. Results of left gastric vena caval shunt for esophageal varices: analysis of one hundred clinical cases. Surgery. 1975;78:628–36.
23. Inokuchi K. A selective portacaval shunt. Lancet. 1968;2:51–2.
24. Millikan WJ Jr, Warren WD, Henderson JM, et al. The Emory prospective randomized trial: selective versus nonselective shunt to control variceal bleeding. Ten year follow-up. Ann Surg. 1985;201:712–22.
25. Rikkers LF, Jin G. Variceal hemorrhage: surgical therapy. Gastroenterol Clin N Am. 1993;22:821–42.
26. Rikkers LF, Sorrell WT, Jin G. Which portosystemic shunt is best? Gastroenterol Clin N Am. 1992;21:179–96.
27. Henderson JM, El Khishen MA, Millikan WJ Jr, Sones PJ, Warren WD. Management of stenosis of distal splenorenal shunt by balloon dilation. Surg Gynecol Obstet. 1983;157:43–8.
28. Warren WD, Millikan WJ Jr, Henderson JM, et al. Splenopancreatic disconnection. Improved selectivity of distal splenorenal shunt. Ann Surg. 1986;204:346–55.
29. Katoh H, Shimozawa E, Kojima T, Tanabe T. Modified splenorenal shunt with splenopancreatic disconnection. Surgery. 1989;106:920–4.
30. Galambos JT, Warren WD, Rudman D, Smith RB III, Salam AA. Selective and total shunts in the treatment of bleeding varices. A randomized controlled trial. N Engl J Med. 1976;295:1089–95.
31. Warren WD, Rudman D, Millikan W, Galambos JT, Salam AA, Smith RB III. The metabolic basis of portasystemic encephalopathy and the effect of selective vs nonselective shunts. Ann Surg. 1974;180:573–9.
32. Yoshida H, Mamada Y, Taniai N, et al. Shunting and nonshunting procedures for the treatment of esophageal varices in patients with idiopathic portal hypertension. Hepatogastroenterology. 2010;57:1139–44.

Chapter 45
Surgical Treatment: Laparoscopic Splenectomy

Makoto Hashizume and Tomohiko Akahoshi

Abstract Portal hypertension is affected by spleen blood flow. An enlarged spleen often increases portal blood flow and pressure. Therefore, splenectomy is an effective surgical management approach for portal hypertension. Laparoscopic surgery has developed in the last two decades. At present, splenectomy is performed laparoscopically. Laparoscopic devascularization of the upper stomach and splenectomy are effective for the treatment of esophageal and gastric varices.

In this study, we introduce the effectiveness and standardized laparoscopic techniques for patients with portal hypertension.

Keywords Splenectomy · Liver cirrhosis · Portal hypertension · Laparoscopic surgery · Esophageal varices · Gastric varices

45.1 Background

Hypersplenism and splenomegaly are common features of patients with portal hypertension that often result in worsening of the condition, leading to pancytopenia, and sometimes causing life-threating variceal hemorrhage. Thus, splenectomy markedly improves the status of portal hypertension by reducing excessive portal flow and mitigating hypocoagulopathy [1].

Recently, laparoscopic surgery has become feasible for surgeons because of advanced laparoscopic devices. Latest clinical studies have shown that laparoscopic splenectomy is not inferior to open splenectomy, even for portal hypertension [2].

M. Hashizume
Department of Surgery, Kitakyushu Chuou Hospital Co., Ltd., Fukuoka, Japan

T. Akahoshi (✉)
Department of Surgery and Science, Kyushu University, Fukuoka, Japan
e-mail: tomohiko@surg2.med.kyushu-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_45

Although laparoscopic surgery causes intraoperative bleeding in laparoscopic splenectomy, it offers preciseness and a clearer surgical field and is less invasive, with the latter accelerating patient's recovery. However, Child-Pugh grade C is a contraindication for this surgery.

45.2 Indications for Laparoscopic Splenectomy

The following criteria are reported as indications for laparoscopic splenectomy in patients with portal hypertension:

1. Platelet count $<3.0 \times 10^4/\mu L$ [1].
2. Resistance to endoscopic treatment for esophageal or gastric varices caused by hypersplenism [3].
3. Gastric varices without major shunt, which are impossible to treat with balloon-occluded retrograde transvenous obliteration (B-RTO) [4].
4. Recovery of platelet count to $<7.0 \times 10^4/\mu L$ on treatment with interferon-based therapy against hepatitis C virus [5].
5. Recovery of platelet count for treatment of malignant tumors, such as surgical intervention and chemotherapy [1, 6].
6. Spleen size $<1000\ cm^3$ (when spleen size > or =$1000\ cm^3$, hand-assisted laparoscopic surgery (HALS) or open surgery should be safe).
7. Child-Pugh grade C (score > or =10) is a contraindication for laparoscopic splenectomy).

45.3 Objectives of Laparoscopic Splenectomy

Patients with portal hypertension have enlarged spleens; therefore, laparoscopic splenectomy is difficult to perform compared with in patients without splenomegaly. The spleen is a highly vascular organ; hence, intraoperative bleeding from the spleen is difficult to stop by hemostat. Attention should be paid to the surrounding developed collateral vessels that are induced by portal hypertension, which might result in significant hemorrhaging during an operation. Thus, preoperative embolization of the splenic artery, placement of a balloon catheter, and intraoperative ligation of the splenic artery have been performed in and reported by several facilities to reduce such a life-threatening complication.

Preoperative degree of splenomegaly, postoperative adhesion, and developed collateral vessels should be examined by computed tomography (CT). HALS should be considered depending on the degree of splenomegaly. The postoperative management for portal vein thrombosis (PVT) and pancreatic leakage is also taken into consideration in this surgery.

45.4 Preoperative Checklist and Management

45.4.1 Blood and Coagulation Examination

The extent of liver damage and pancytopenia should be checked before surgery. Platelet transfusion is recommended immediately prior to surgery in cases of thrombocytopenia. If prothrombin time decreases to less than 60%, transfusion of fresh frozen plasma is also recommended.

45.4.2 Preoperative CT Examination

Spleen size and splenic artery and vein formation should be assessed before surgery. Spleen size is an important factor in determining the difficulty of a laparoscopic splenectomy. The diameter of the splenic vein is another important parameter for preventing portal vein thrombosis. Thus, the development of collateral vessels must be considered to avoid intraoperative hemorrhage. An estimated spleen size of >1000 cm^3 and large collateral vessels should be considered when performing HALS. In cases of poor liver function, such as Child-Pugh grade B $\geq$ 9, HALS is a better option.

45.4.3 Surgical Devices to Prepare for Laparoscopic Splenectomy

The following devices are necessary to perform a laparoscopic surgery in patients with portal hypertension:

1. Ultrasonic incision device (ultrasonically activated device).
2. Vessel-sealing device (LigaSure™ and Enseal™) and autosuture device (e.g., Echelon 60™).
3. A nylon sac (Endocatch II™) that is larger than normal for an enlarged spleen.

45.5 Anesthesia and Operative Position

General anesthesia is administered. Epidural anesthesia is often contraindicated because of the ease of bleeding in patients with portal hypertension.

The patient is usually positioned in the right semi-decubitus position. Magic beds are used to rotate the operative bed freely (Fig. 45.1).

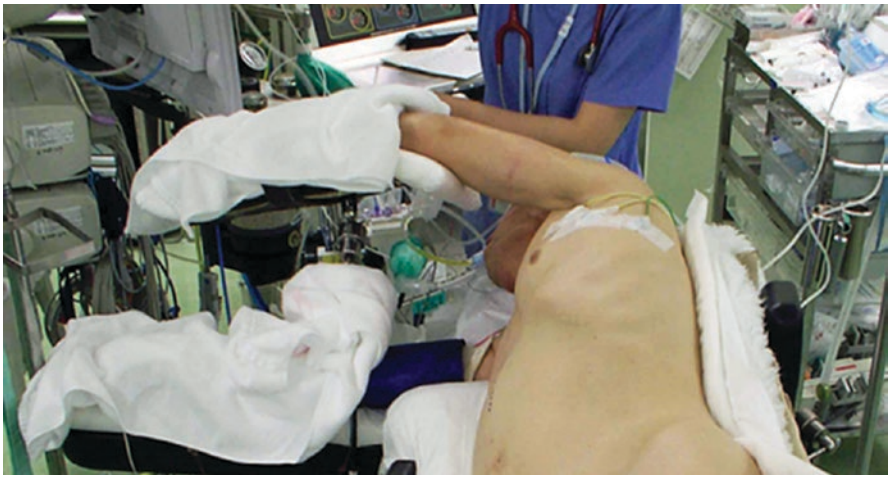


Fig. 45.1 Operative position. Patient is usually positioned in the right semi-decubitus position. Fixation by magic bed; a lateral plate allows the bed to rotate freely

45.5.1 Skin Incision and Insertion of Trocars

Four trocars (5–12 mm) are inserted under visual control into the left side of the abdomen. First, a 12-mm trocar is usually inserted into the left side of the umbilicus by open laparotomy and then used as a laparoscopic port. Next, a 5-mm trocar is inserted into the epigastric fossa. Finally, the other two 12-mm trocars are inserted into the midclavicular and middle axillary lines of the left subcostal area. During HALS, a 6–7-cm skin incision is made in the midline of the upper abdomen, and a lap disk is attached (Fig. 45.2).

45.5.2 Surgical Procedure

45.5.2.1 Dissection of the Left Lateral Area of the Spleen (Fig. 45.3a, b)

Initially, the splenic ligament of the lower pole of the spleen is dissected. The lower branch of the splenic artery and vein is encountered in this area. Gentle and accurate maneuvering is necessary (Fig. 45.3a). Then, the lateral ligament of the spleen is dissected toward the upper pole of the spleen using an ultrasonic incision device (splenorenal and splenophrenic ligaments) (Fig. 45.3b). The laparoscopic view is superior to open surgery in this field. The vessels in the lateral ligament of the spleen are hardly developed, rendering it easy to dissect without a vessel-sealing system.

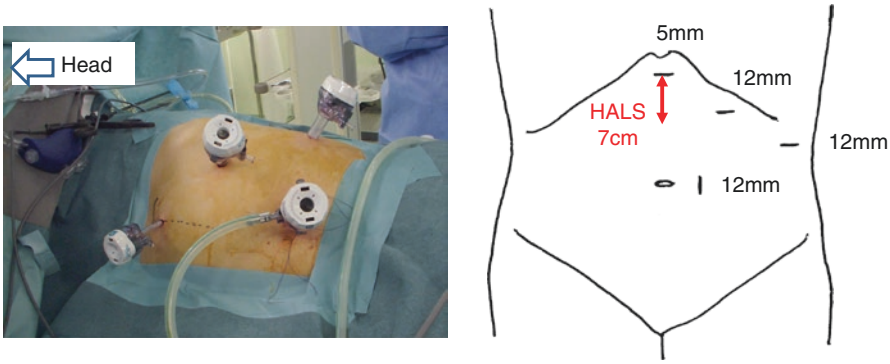


Fig. 45.2 Skin incision and trocar positions. Laparoscopic splenectomy is performed using four ports. In the case of HALS, an approximately 7-cm incision was made

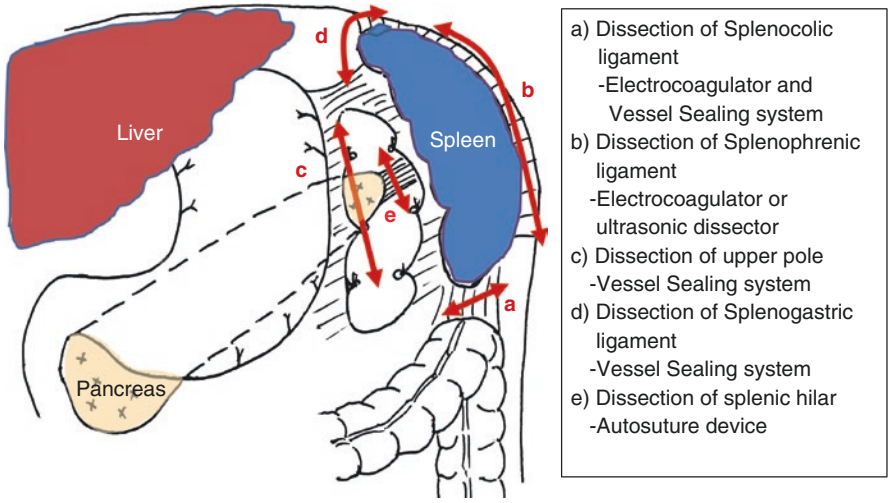


Fig. 45.3 Surgical procedure. The surgical procedure consists of five parts

45.5.2.2 Dissection of the Gastrosplenic Ligament (Fig. 45.3c–e)

Mobilizing the spleen in a lateral direction and grasping the stomach expose the gastrosplenic ligament (Fig. 45.3c). The omental bursa is opened by entering from an area of the omentum without vessels. The exposure of the hilum is completed by dividing the transparent window of the splenogastric ligaments using a vessel-sealing device. In most patients, the gastrosplenic ligament near the upper pole of the spleen is crowded because of the enlarged spleen and developed collateral vessels; thus, careful dissection is necessary (Fig. 45.3d). An autosuture device is useful for dissection of enlarged collateral vessels or short gastric veins with a diameter of >7 mm.

45.5.2.3 Dissection of Splenic Hilum (Fig. 45.3e)

The tissues around the splenic hilum, including the splenic arteries and veins, are cut using an autosuture device. Before cutting the splenic hilum, the surgeon should confirm that the pole of the spleen has been raised from the surrounding tissue, which makes an autosuture device is safely applied to the splenic hilum. The splenic hilum is divided by a single dissection using an autosuture device in most cases. However, second or third dissections can be necessary for large spleens. In such cases, the operator must strive to dissect as much of the hilum as possible in the initial dissection. Otherwise, a resection that is performed only halfway can lead to life-threatening bleeding from the splenic hilum. It is dangerous to dissect when the tip of the autosuture device does not reach the end of the splenic hilum, in which case dissection of the lower branch of the splenic artery and vein should be considered.

The cut line should also be as close to the spleen as possible to prevent pancreatic leakage. Total laparoscopic surgery should not be applied in cases of unsafe dissection. Conversion to HALS or open surgery is a better option. If uncontrollable bleeding occurs, surgeons should not hesitate to convert to HALS or open surgery.

45.5.2.4 Spleen Retrieval

After the spleen is resected, it is put into a plastic bag (Endocatch II; Tyco Healthcare, Tokyo, Japan) and cut into pieces using scissors. The fractured spleen is removed from the abdominal cavity through the skin incision site in the umbilicus, without any extension of the wound.

45.5.2.5 Hemostasis and Drain Insertion

Bleeding from the staple line should be addressed. Veriplaset P™ and/or TachoSil™ is available for the prevention of postoperative bleeding and pancreatic leakage. A closed drain is positioned in the subphrenic area to detect postoperative bleeding and pancreatic leakage.

45.6 HALS Splenectomy

Given the known risk of conversion to open surgery in laparoscopic splenectomy, as reported by our group and others, preoperative CT should be performed in each patient to assess the spleen size and development of collaterals surrounding the spleen and to determine whether HALS is appropriate. In patients with developed collateral vessels or a large spleen (estimated volume of >1000 mm^3), HALS is recommended at the outset of the laparoscopic splenectomy [7].

45.7 Prevention and Treatment of Postoperative Complication

45.7.1 Postoperative Bleeding

In cases of bleeding tendencies, drain output should be monitored, and a blood examination should be performed. If there is no bleeding, the patient can get out of bed and resume usual oral intake on the next day after surgery.

45.7.2 Pancreatic Leakage

The level of drain amylase should be measured irrespective of whether a pancreatic injury occurs. It might be better to delay extraction of the abdominal drain after confirmation of a pancreatic fistula. Usually, only fasting recovers amylase levels to normal [8].

45.7.3 Portal Vein Thrombosis

PVT is one of most significant complications of splenectomy in patients with portal hypertension. According to our research, spleen weight and splenic vein diameter are significant risk factors after splenectomy [9]. Antithrombin III (AT-III) is also a reliable marker of PVT after splenectomy [10]. Therefore, AT-III is an effective drug for the prevention of PVT. Caution should be taken in patients with spleens that exceed 500 g. PVT is diagnosed by abdominal echo and CT. D-dimer and fibrin degradation product (FDP) levels are also helpful in examining D-dimer and FDP formation. If PVT is found by abdominal echo or CT, anticoagulation therapy should be initiated carefully. Unfractionated heparin or AT-III may be effective in preventing PVT in high-risk patients. Once PVT develops, anticoagulation therapy should be continued until it disappears.

45.7.4 Overwhelming Postsplenectomy Infection

Overwhelming postsplenectomy infection (OPSI) is a rare but rapidly fatal infection that occurs after splenectomy. It is typically characterized by meningitis or sepsis and is caused by encapsulated organisms, including *Streptococcus pneumoniae*. Most infections occur in the first several years following splenectomy, but the risk of OPSI exists for life. OPSI is nearly uniformly fatal without treatment, and modern treatments have decreased the resulting mortality rates to approximately 40–70%. Individuals with OPSI are most commonly treated with antibiotics and supportive care. Therefore, regular vaccination and early prophylactic antibiotics

should be given to prevent OPSI. Education for splenectomized patients has also been reported to be useful for preventing OPSI.

45.8 Benefits of Splenectomy in Patients with Portal Hypertension

45.8.1 Decompression of Portal Vein Pressure

On average, hepatic vein wedge pressure decreases by 24% in patients who undergo splenectomy, due to spleen weight (Fig. 45.4).

45.8.2 Improvement in Hypersplenism

The most significant benefit of splenectomy in patients with hypersplenism is the improvement in pancytopenia. Platelet and white blood cell counts are significantly increased at 14 days after the surgery (Fig. 45.5). The improvement in pancytopenia is maintained in the long term [1].

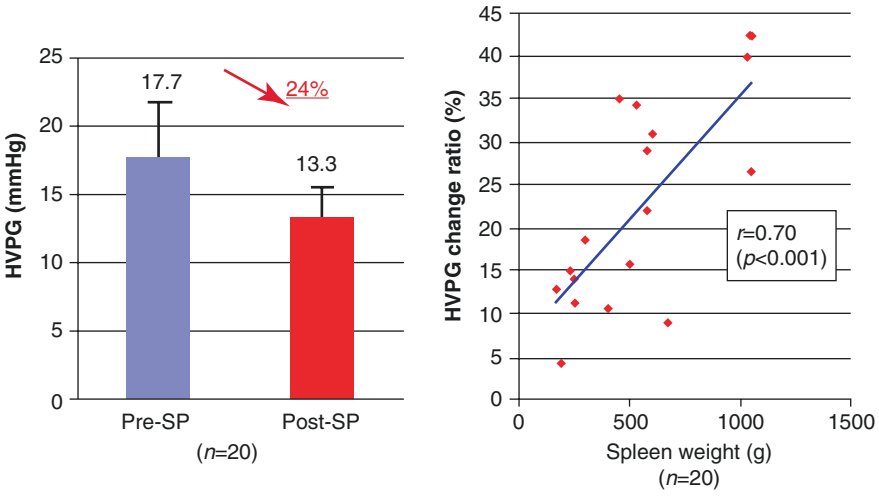


Fig. 45.4 Decompression of portal vein pressure after splenectomy

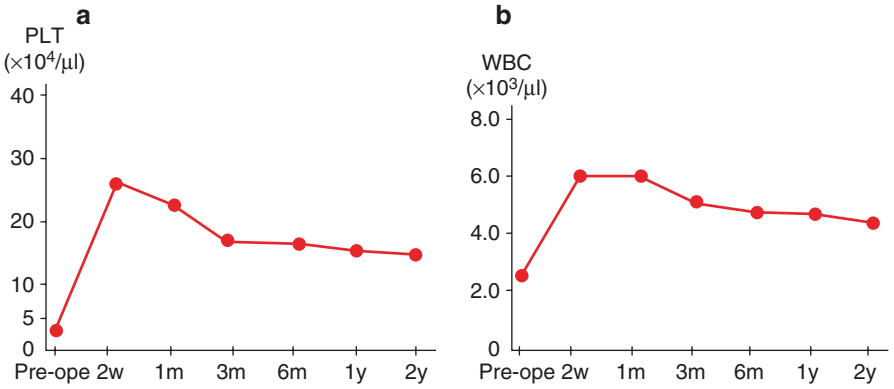


Fig. 45.5 (**a**) Long-term change in platelet count after laparoscopic splenectomy (n = 60) (2w, 2 weeks after splenectomy; m, month; y, year). (**b**) Long-term change in platelet count after laparoscopic splenectomy (n = 60) (2w, 2 weeks after splenectomy; m, month; y, year)

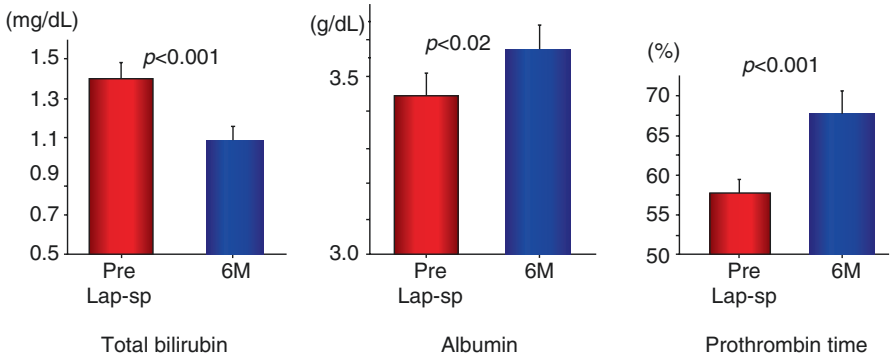


Fig. 45.6 Changes in liver function following laparoscopic splenectomy. (*Lap-sp* laparoscopic splenectomy, *Pre* preoperation, *6M* 6 months after splenectomy)

45.8.3 Improved Liver Function

In most patients with cirrhosis, there is significant improvement in total bilirubin and percent prothrombin time activity after laparoscopic splenectomy (Fig. 45.6).

45.9 Laparoscopic Devascularization of the Upper Stomach and Splenectomy (Hassab's Operation)

There are several effective nonsurgical approaches to treat esophageal variceal bleeding. However, certain patients have endoscopy-resistant esophageal varices. In addition, bleeding from gastric varices remains a therapeutic challenge. In such situations, operative management is sometimes required.

Since Hassab's first description of devascularization and splenectomy in patients with portal hypertension, this procedure has become one of the most effective surgical procedures for esophagogastric varices, with some modifications. This procedure is currently performed for endoscopy-resistant patients and gastric varices in many facilities worldwide because of its feasibility and less invasive nature compared with shunt surgery or transplantation.

45.9.1 Surgical Procedure

As shown in Fig. 45.1, the surgical procedure for Lap-Dev + Sp or HALS-Dev + Sp comprises three dissections: that in splenectomy and of short gastric veins, greater curvature vessels, and left gastric artery and vein and lesser curvature vessels (Fig. 45.7).

45.9.2 Dissection in Splenectomy and Short Gastric Veins (Fig. 45.7a)

Laparoscopic splenectomy was performed as described in the previous section on splenectomy. In most patients, the gastrosplenic ligament near the upper pole of the spleen was crowded because of the enlarged spleen and developed collateral vessels that require careful dissection. In cases of enlarged collateral vessels or short gastric veins with a diameter of >7 mm, the Endo GIA™ (COVIDIEN, Tokyo, Japan) was used for dissection.

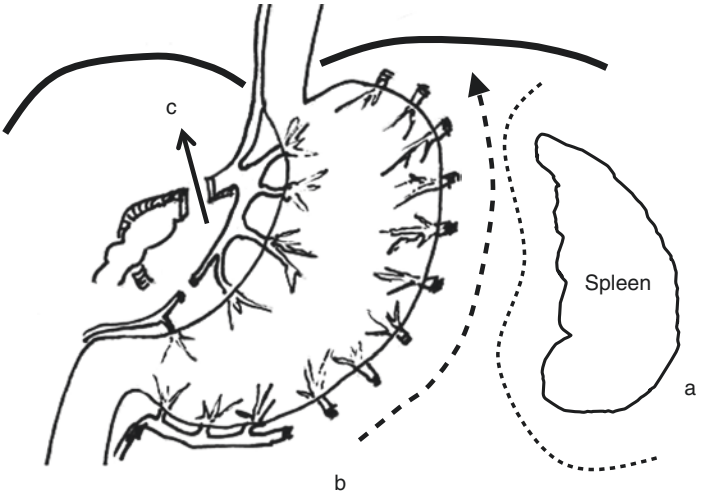


Fig. 45.7 Surgical procedure for Lap-Dev + Sp or HALS-Dev + Sp. Surgical procedure consists of three parts: dissection of the splenectomy and short gastric veins, greater curvature vessels, and left gastric artery and vein and lesser curvature vessels

45.9.3 Dissection of the Greater Curvature Vessels, Left Gastric Artery and Vein, and Lesser Curvature Vessels (Fig. 45.7b, c)

Dissection of the gastrosplenic ligament toward the pylorus was performed. After sufficient dissection of the greater curvature vessels, the stomach was pulled toward the abdominal wall. Next, the lesser omentum was dissected, and the left gastric artery and vein were recognized through the back of the stomach and divided by Echelon (white cartridge; Ethicon Endo-Surgery, Cincinnati, OH) (Fig. 45.8a, b). The lesser curvature vessels toward the esophagus were dissected using LigaSure Atlas EnSeal. In some cases, ligation and an autosuture device are necessary when the encountered collateral vessels are >7 mm.

45.10 Surgical Results

All high-risk gastric varices were eradicated or diminished into small gastric varices (F1) without red spots in all 15 patients, according to general rules for recording endoscopic findings of esophagogastric varices [4] (Fig. 45.9). Endoscopy-resistant esophageal varices were also downsized to low-risk esophageal varices (Fig. 45.10a, b). All residual varices were treated easily by endoscopic variceal ligation or endoscopic injection sclerotherapy and eradicated in one or two sessions after the operation (Fig. 45.10c).

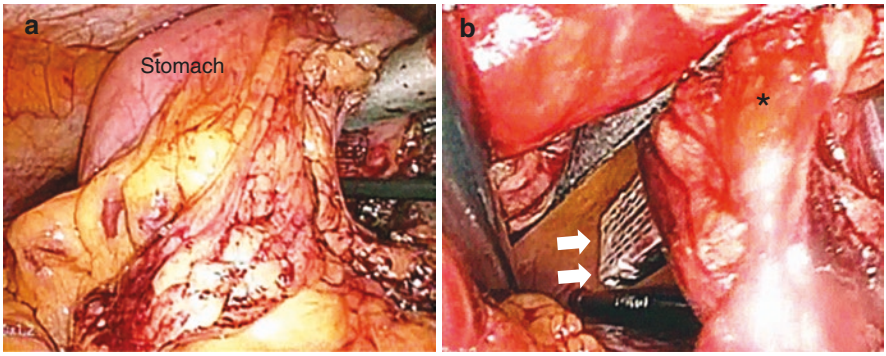


Fig. 45.8 Representative intraoperative findings. The trunk of the gastric vessels, including the left artery and vein, was dissected using an autosuture device (*arrow*) through the back of the stomach. Asterisk—left gastric artery and vessels

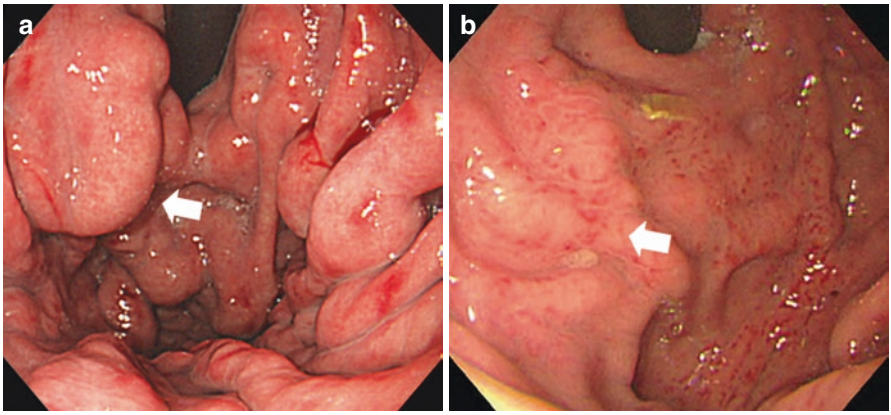


Fig. 45.9 Representative endoscopic findings of the stomach before and after surgery. (**a**) Tumorous gastric varices (F3) with red spots were recognized (*arrow*). (**b**) After HALS-Dev + Sp, the tumorous varices disappeared (*arrow*)

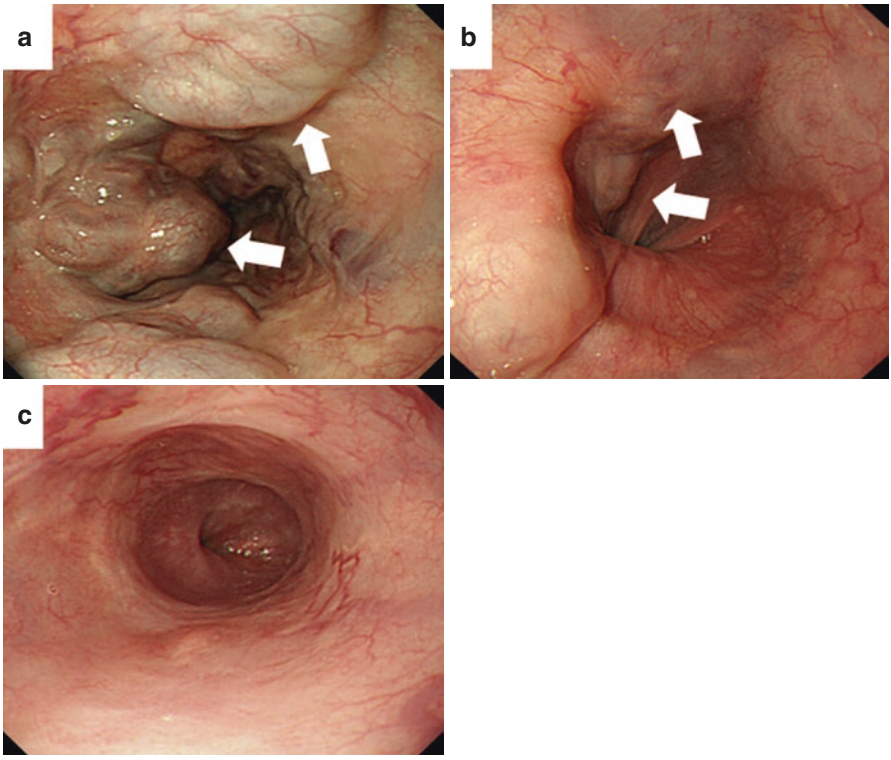


Fig. 45.10 Endoscopic findings of the esophagus. (**a**) Large, high-risk esophageal varices (F3CwRC2+) were recognized (*arrow*). (**b**) The large esophageal varices were decreased into small varices without red color (*arrow*) 1 week after HALS-Dev + Sp. (**c**) After two sessions of endoscopic variceal ligation, the esophageal varices were eradicated

References

1. Hashizume M, Tomikawa M, Akahoshi T, et al. Laparoscopic splenectomy for portal hypertension. Hepatogastroenterology. 2002;49(45):847–52.
2. Hashizume M, Sugimachi K, Ueno K. Laparoscopic splenectomy with an ultrasonic dissector. N Engl J Med. 1992;327(6):438.
3. Hashizume M, Tanoue K, Morita M, et al. Laparoscopic gastric devascularization and splenectomy for sclerotherapy-resistant esophagogastric varices with hypersplenism. J Am Coll Surg. 1998;187(3):263–70.
4. Akahoshi T, Uehara H, Tomikawa M, et al. Comparison of open, laparoscopic, and hand-assisted laparoscopic devascularization of the upper stomach and splenectomy for treatment of esophageal and gastric varices: a single-center experience. Asian J Endosc Surg. 2014;7(2):138–44.
5. Akahoshi T, Tomikawa M, Korenaga D, et al. Laparoscopic splenectomy with peginterferon and ribavirin therapy for patients with hepatitis C virus cirrhosis and hypersplenism. Surg Endosc. 2010;24(3):680–5.
6. Shimada M, Hashizume M, Shirabe K, et al. A new surgical strategy for cirrhotic patients with hepatocellular carcinoma and hypersplenism. Performing a hepatectomy after a laparoscopic splenectomy. Surg Endosc. 2000;14(2):127–30.
7. Kawanaka H, Akahoshi T, Kinjo N, et al. Technical standardization of laparoscopic splenectomy harmonized with hand-assisted laparoscopic surgery for patients with liver cirrhosis and hypersplenism. J Hepatobiliary Pancreat Surg. 2009;16(6):749–57.
8. Tsutsumi N, Tomikawa M, Akahoshi T, et al. Pancreatic fistula after laparoscopic splenectomy in patients with hypersplenism due to liver cirrhosis: effect of fibrin glue and polyglycolic acid felt on prophylaxis of postoperative complications. Am J Surg. 2016;212(5):882–8.
9. Kinjo N, Kawanaka H, Akahoshi T, et al. Risk factors for portal venous thrombosis after splenectomy in patients with cirrhosis and portal hypertension. Br J Surg. 2010;97(6):910–6.
10. Kawanaka H, Akahoshi T, Kinjo N, et al. Impact of antithrombin III concentrates on portal vein thrombosis after splenectomy in patients with liver cirrhosis and hypersplenism. Ann Surg. 2010;251(1):76–83.

Part IV
Complications of Portal Hypertension: Portal Hypertensive Gastroenteropathy

Chapter 46
Diagnosis and Endoscopic Classification of Portal Hypertensive Gastroenteropathy

Kazuhiko Oho

Abstract Changes other than varices frequently occur in the gastrointestinal mucosa in patients with portal hypertension. They are portal hypertensive gastropathy, portal hypertensive colopathy, and portal hypertensive enteropathy. All of these are non-inflammatory, and the main change is in vascular congestion. These changes occasionally cause acute or chronic gastrointestinal hemorrhage, which are clinically important. Observation of the entire digestive tract has become relatively easy with the recent development of video capsule endoscopy and balloon enteroscopy, and the pathology of portal hypertensive gastroenteropathy is being elucidated.

Keywords Portal hypertensive gastropathy · Portal hypertensive colopathy · Portal hypertensive enteropathy · Rectal varices · Angiodysplasia

46.1 Introduction

Gastrointestinal mucosal changes other than varices are frequently observed in patients with portal hypertension. These are termed as portal hypertensive gastroenteropathy (PHGE). Portal hypertensive gastropathy (PHG) [1], portal hypertensive colopathy (PHC) [2], and portal hypertensive enteropathy (PHE) [3] are included, and congestion is the main change. These are clinically important because they cause acute and chronic gastrointestinal hemorrhage.

In this section, PHGE is outlined, and its diagnosis and endoscopic classification are explained.

K. Oho
Kurume University School of Medicine, Fukuoka, Japan

Department of Gastroenterology and Hepatology, Yanagawa Hospital, Fukuoka, Japan
e-mail: k-oho@yanagawa-hsp.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_46

46.2 Portal Hypertensive Gastropathy

46.2.1 Cause

The main change in PHG is portal blood pressure elevation-induced congestion in the gastric mucosa. Histologically, dilation and edema of capillary blood vessels in the mucosal layer and veins in the submucosal layer are characteristic. Unlike gastritis, no inflammatory cell infiltration is observed in PHG [4, 5], and gastric acid, alcohol, or *Helicobacter pylori* are not involved [6, 7]. The relationship between PHG and the severity of underlying liver disease is controversial. Some investigators found a close correlation between PHG and the severity of the Child-Pugh score [8, 9], but others observed only a weak correlation between the severity of PHG and underlying liver cirrhosis. The etiologic mechanism of PHG is not completely understood, but the regulation of nitric monoxide, endothelin-1, and TNF-α in the stomach may be involved [10–12].

On the other hand, the severity of PHG was mild in patients with a developed gastro-renal shunt on portography [13], and the grade of PHG aggravation following occlusion of esophageal varices was mild [14], suggesting that the presence of a gastro-renal shunt was a factor inhibiting PHG.

This observation was explained by the following: development of a gastro-renal shunt, which is the outlet of gastric varices, inhibits internal pressure elevation of the posterior or short gastric vein, which is the blood-supplying route, and subsequently prevents congestion in the gastric mucosa.

46.2.2 Diagnosis and Endoscopic Classification of PHG

PHG is diagnosed by upper gastrointestinal endoscopy. In general, the classification established by McCormack et al. [4] is used for endoscopic findings (Table 46.1). In this endoscopic classification, five findings are divided into two groups (mild and severe PHG groups): (1) fine pink speckling, (2) superficial reddening, and (3) snakeskin appearance (SSA) are classified as mild, and (4) cherry red spots (CRS) and (5) diffuse hemorrhage (DH) are classified as severe. However, whether fine pink speckling, which is considered the mildest finding, reflects portal hypertension remains controversial.

Superficial reddening represents a state in which edema is mild, and the capillary blood vessels and clustered venules are dilated, rendering the surface red-

Table 46.1 McCormack's classification

Mild gastropathy	Fine pink speckling
	Superficial reddening
	Snakeskin appearance (mosaic pattern)
Severe gastropathy	Cherry red spots
	Diffuse hemorrhage

dish. SSA represents a state of the gastric area appearing small whitish demarcation due to edema, in addition to dilation of capillary blood vessels and clustered venules that resemble whitish snake scales (Fig. 46.1). Cherry red spots represent a state in which whitish regions increase, capillary blood vessels become less noticeable with progression of edema, and only clustered venules are noticeable (Fig. 46.2). Diffuse hemorrhage may be due to breakthrough bleeding in the mucosa (Fig. 46.2). Of these features, the typical endoscopic finding most frequently encountered is SSA, and this is synonymous with mosaic pattern in other reports [15].

In Europe, to eliminate differences in interpretation among original diagnostic criteria, diagnostic guidelines have been published by the New Italian Endoscopic Club for the Study and Treatment of Oesophageal Varices (NIEC) in 1992 [16], in which the evaluation of endoscopic findings as PHG was validated: The mosaiclike pattern, i.e., SSA in the McCormack criteria, is the most specific finding reflecting mild PHG, and is frequently observed in the fundus over the corpus of the stomach, with a low risk of hemorrhage. When diffuse red marks are observed, the risk of hemorrhage is high, reflecting severe PHG, whereas hemorrhage is unlikely when red marks are localized.

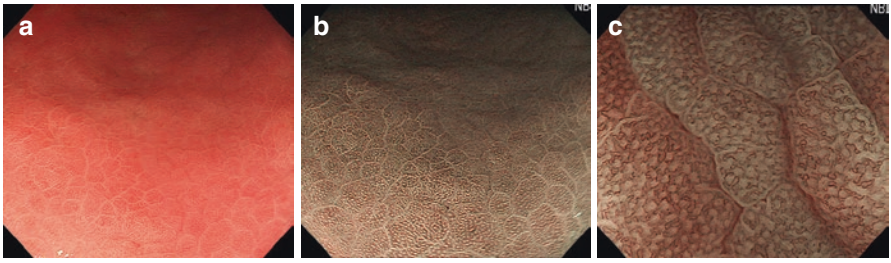


Fig. 46.1 Portal hypertensive gastropathy (mild). Snakeskin appearance. (**a**) White light image. (**b**) Narrow-band imaging (NBI). (**c**) Magnified view of NBI

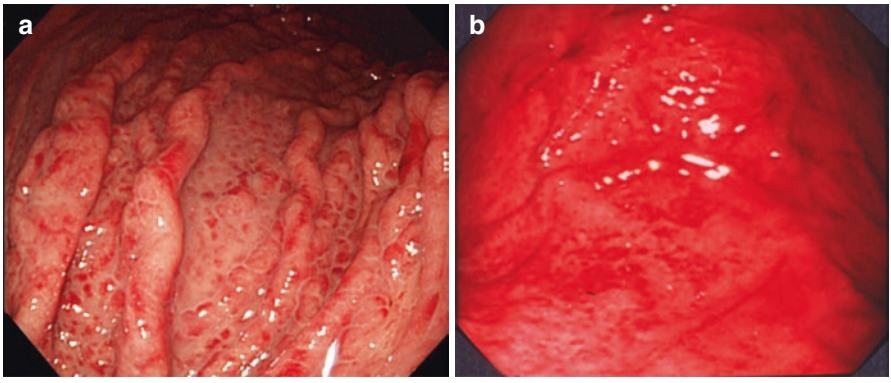


Fig. 46.2 Portal hypertensive gastropathy (severe). (**a**) Cherry red spots. (**b**) Diffuse hemorrhage

Table 46.2 Toyonaga's classification

Grade 1	Erythematous flecks or macula
Grade 2	Red spots, diffuse redness
Grade 3	Intramucosal or luminal hemorrhage

Snakeskin appearance is universally observed at all grades

In Japan, Toyonaga et al. examined the grade of congestion in PHG using the organ reflectance spectrum-analyzing method and classified it into three grades: Grade 1, mild, punctate/patchy redness (erythematous flecks or macula); Grade 2, intermediate, red spots or diffuse redness; and Grade 3, severe, hemorrhagic (intramucosal or luminal hemorrhage). SSA is regarded as a finding universally observed at all grades [17] (Table 46.2).

Endoscope apparatuses equipped with image-enhancing observation functions using a specific wavelength range as an endoscope light utilizing the optical characteristics of biological tissue, such as narrow-band imaging (NBI) using a blue narrow-band illumination light and infrared imaging (IRI) using infrared light, have recently been used in clinical practice. NBI is superior in PHG observation because it highlights capillary blood vessels in the superficial layer of the mucosa and microstructures on the mucosal surface (pit pattern) [18] (Fig. 46.1).

46.2.3 Frequency

The frequencies of mild and severe PHG have been reported to be 20–94% and 7–41%, respectively [4, 6, 19–21], and this variation may be due to differences in subjects or observer errors. However, the snakeskin (mosaic) pattern was consistently the most frequent observation in mild PHG [6, 19, 20]. As PHG with small changes may aggravate, improve, or disappear, lesions should be carefully observed by endoscopy [21, 22]. In addition, the frequency of hemorrhagic cases has been reported to be 4–40% [4, 6, 21], and most cases were due to severe PHG.

46.2.4 Influence of Treatment on Varices

Endoscopic treatment of varices is performed not only for hemorrhagic cases but also for prophylactic and elective cases by sclerotherapy and/or ligation of varices. In endoscopic treatment of esophageal varices, the varices disappear following the occlusion of the blood-supplying veins. Accordingly, endoscopic treatment further promotes congestion in the gastric mucosal hemodynamics, and PHG is aggravated in many cases [4, 6, 21, 22]. However, aggravation of PHG after endoscopic treatment is mild in many cases with well-developed varices in the gastric fundus [14] because the major shunt inhibits PHG, as described above.

46.3 Portal Hypertensive Colopathy and Enteropathy

In patients with portal hypertension, characteristic mucosal changes occur not only in the stomach but also in the duodenum and small and large intestines. PHC was discovered early [23]. The presence of PHE was clarified with the spread of small intestinal balloon endoscopy and capsule endoscopy [24, 25].

The histological characteristics of these lesions are mainly vasodilation and edema in the mucosal and submucosal layers, and inflammatory cell infiltration is absent, which are similar to those in PHG [23, 26].

46.3.1 Portal Hypertensive Colopathy

46.3.1.1 Epidemiology of PHC

The term PHC was initially described in 1991 in a study reporting that vasodilation in the colon and rectal varices was a portal hypertension-associated endoscopic characteristic [23].

The prevalence of PHC in cirrhotic patients ranged from 3 to 84%, and the frequency of bleeding in patients with PHC was estimated to be 0–9%. These differences in the prevalence and risk of hemorrhage among previous reports may be due to the patient selection, study design, or absence of an established classification system.

The relationship between PHC and the severity of liver disease is controversial. PHC is considered to be associated with severe liver disease diagnosed according to Child-Pugh scoring [27, 28], presence of large esophageal varices [28, 29], and high portal blood pressure [30], whereas other studies reported the absence of an association between PHC and severe Child-Pugh score [31], portal blood pressure [32], liver stiffness value [31], or presence of gastroesophageal varices [33]. However, an increase in the frequency of PHC by endoscopic treatment of esophageal varices has been noted [23], suggesting involvement of portal blood pressure in the development of PHC. Yamakado et al. established an original severity classification based on the number of vascular ectasia and observed a favorable correlation with portal blood pressure [29].

46.3.1.2 Diagnosis and Endoscopic Classification of PHC

PHC is diagnosed by endoscopy. No classification system for grading the severity of PHC is available. Vascular changes, such as angiodysplasia-like lesions, solitary or diffuse cherry red spots, and colorectal varices, have been reported as colonoscopic findings of PHC accompanying liver cirrhosis [26, 29] (Figs. 46.3 and 46.4).

Several endoscopic classifications have been proposed (Table 46.3) [28, 29]. According to these classifications, endoscopic findings of PHC are classified into: (1) vascular lesions, (2) nonvascular or colitis-like lesions, or (3) rectal varices. Of these, vascular lesions are the most frequently observed.

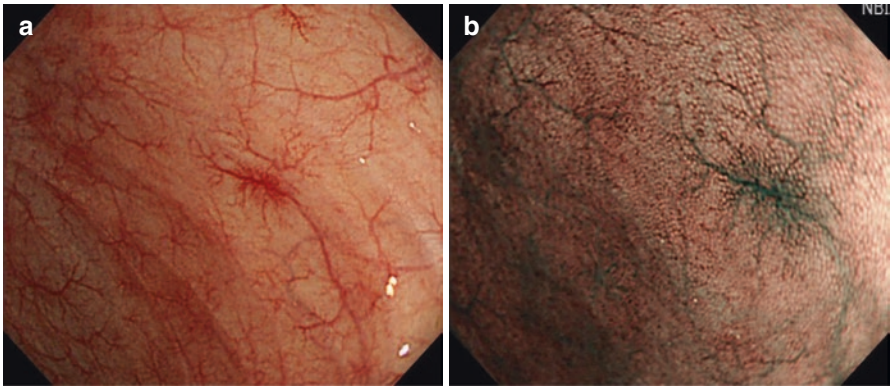


Fig. 46.3 Portal hypertensive colopathy. Angiodysplasia-like lesions. (**a**) White light image. (**b**) Narrow-band imaging (NBI)

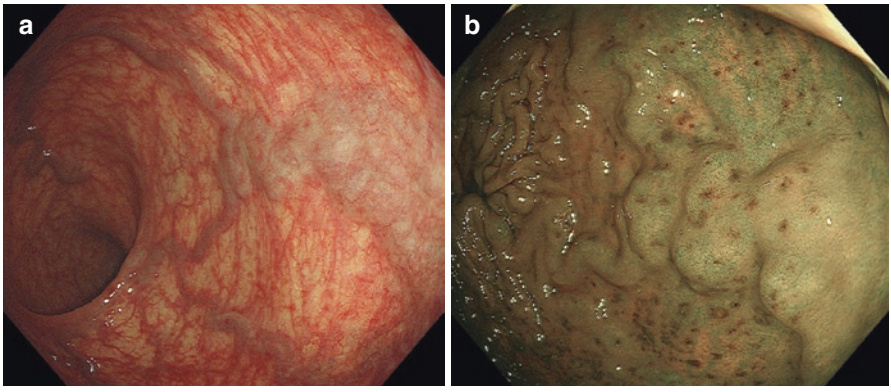


Fig. 46.4 Portal hypertensive colopathy. Rectal varices and vascular ectasia in the rectum. (**a**) White light image. (**b**) Narrow-band imaging (NBI)

Table 46.3 Endoscopic definition for portal hypertensive colopathy

	Yamakado et al. [29] (1995)	Bini et al. [28] (2000)
Definition of PHC	Vascular ectasia Vascular irregularities Vascular dilatation (>3 mm vein including colonic and rectal varices) Solitary red spots Diffuse red spots Hemorrhoids	Colitis-like abnormalities (edema, erythema, granularity, friability, and/or spontaneous bleeding) Vascular lesions (cherry red spots, telangiectasias, or angiodysplasia-like lesions) Rectal varices, hemorrhoids

PHC portal hypertensive colopathy

Findings other than rectal varices are not specific for portal hypertension and may be observed in patients without portal hypertension. It is important to diagnose PHC following sufficient consideration of the patient background.

46.3.2 Portal Hypertensive Enteropathy

46.3.2.1 Epidemiology of PHE

Changes in the jejunal and ileal mucosa have been discussed after portal hypertension-associated mucosal changes in the stomach, and the large intestine was clarified. The recent introduction of video capsule endoscopy (VCE) and balloon enteroscopy has enabled close observation of the entire small intestinal region, and these techniques are very useful for recognizing and understanding small intestinal changes in portal hypertension [24, 25].

The frequency of PHE widely varies from 15 to 82% among observers, and this may be largely due to differences in the clinical severity of the subject patients and development of observation means.

The frequency of bleeding in PHE has not yet been clarified.

Developed esophageal varices, history of treatment of esophageal varices with sclerotherapy and/or ligation, PHC, PHG, and Child-Pugh class C have been reported as clinical parameters related with PHE [24, 34]. Of these, associations of the severity of liver disease (Child-Pugh C) and presence of PHG with PHE are consistent among most studies.

46.3.2.2 Diagnosis and Endoscopic Classification of PHE

PHE is endoscopically diagnosed by VCE and balloon enteroscopy.

Similar with the PHC classification described above, endoscopic findings of PHE (Fig. 46.5) are classified into: (1) vascular lesions, (2) nonvascular or colitis-

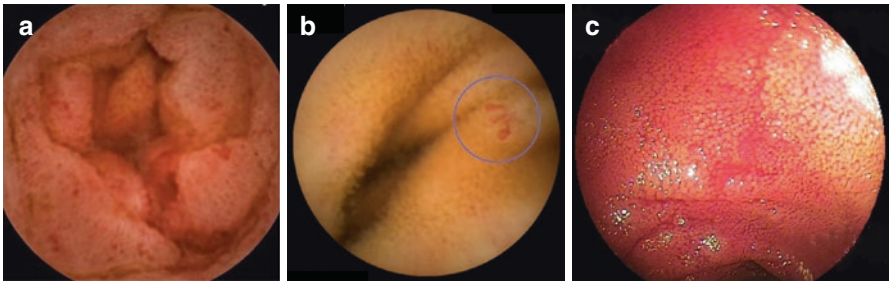


Fig. 46.5 Portal hypertensive enteropathy. (**a**) Vascular lesions (red spots) found during video capsule endoscopy (VCE). (**b**) Vascular lesions (vascular ectasia) found during VCE. (**c**) Colitis-like lesions found during balloon enteroscopy

Table 46.4 Endoscopic definition for portal hypertensive enteropathy

	DePalma et al. [24] (2005)	Kodama et al. [25] (2008)
Method	Video capsule endoscopy	Double-balloon endoscopy
Definition of PHE	Inflammatory-like abnormalities Vascular lesions (telangiectasias or angiodysplastic-like lesions, red spots) Varices	Villous abnormality (edema, atrophy, and reddening for villous abnormalities) Vascular lesions (angiodysplasia-like lesions, dilated or proliferated vessels, varices)

PHE portal hypertensive enteropathy

like lesions, or (3) varices (Table 46.4). Of these, the frequency of vascular lesions has been reported to be higher than those of the others [24]. In a study using double-balloon enteroscopy reported by Kodama et al. [25], PHE lesions were classified into two categories, villous abnormalities and vascular lesions, and each category was further classified into three subtypes: (1) edema, atrophy, and reddening for villous abnormalities, (2) angiodysplasia-like lesions and dilated or proliferated vessels, and (3) varices for vascular lesions. Villous changes may be characteristic for PHE and are absent in PHG and PHC.

46.4 Summary

In patients with portal hypertension, noninflammatory changes appear in the entire gastrointestinal mucosa, and these changes are important because they may cause acute or chronic gastrointestinal hemorrhage. To identify the hemorrhagic region, it is necessary to be familiar with the endoscopic characteristics of PHG, PHC, and PHE.

References

1. Tarnawaski A, Sarfeh IJ, Stachura J, Hajduczek A, But HX, Dabros W, et al. Microvascular abnormalities of the portal hypertensive gastric mucosa. Hepatology. 1988;8:1488–94.
2. Kozarek RA, Botoman VA, Bredfeldt JE, Roach JM, Patterson DJ, Ball TJ. Portal colopathy: prospective study of colonoscopy in patients with portal hypertension. Gastroenterology. 1991;101:1192–7.
3. Tang SJ, Jensen DM, Gralnek IM, Roth BE. Portal hypertensive enteropathy in a patient with polycystic liver disease: a unique endoscopic finding. Gastrointest Endosc. 2002;56:924–6.
4. McCormack TT, Sims J, Eyre-Brook I, Kennedy H, Goepel J, Johnson AG, et al. Gastric lesion in portal hypertension: inflammatory gastritis or congestive gastropathy? Gut. 1985;26:1226–32.
5. Triger DR, Hosking SW. The gastric mucosa in portal hypertension. J Hepatol. 1989;8:267–72.
6. D'Amico G, Montalbano L, Traina M, Pisa R, Menozzi M, Spanò C, et al. Natural history of congestive gastropathy in cirrhosis. The Liver Study Group of V. Cervello Hospital. Gastroenterology. 1990;99:1558–64.

7. Bahnacy A, Kupcsulik P, Eles Z, Jaray B, Flautner L. Helicobacter pylori infection in congestive gastropathy. Helicobacter. 1996;1:168–71.
8. Iwao T, Toyonaga A, Sumino M, Takagi K, Oho K, Nishizono M, et al. Portal hypertensive gastropathy in patients with cirrhosis. Gastroenterology. 1992;102:2060–5.
9. Teranto D, Suozzo R, Romano M, di Sapio M, Caporaso N, Del Vecchio BC, et al. Gastric endoscopic features in patients with liver cirrhosis: correlation with esophageal varices, intravariceal pressure, and liver dysfunction. Digestion. 1994;55:115–20.
10. Migoh S, Hashizume M, Tsugawa K, Tanoue K, Sugimachi K. Role of endothelin-1 in congestive gastropathy in portal hypertensive rats. J Gastroenterol Hepatol. 2000;15:142–7.
11. Ohta M, Tanoue K, Tarnawski A, Pai R, Itani RM, Sander FC, et al. Overexpressed nitric oxide synthase in portal-hypertensive stomach of rat: a key to increased susceptibility to damage? Gastroenterology. 1997;112:1920–30.
12. Munoz J, Albillos A, Perez-Paramo M, Rossi I, Alvarez-Mon M. Factors mediating the hyperdynamic effects of tumor necrosis factor-alpha in portal hypertensive rats. Am J Phys. 1999;276:687–93.
13. Iwao T, Toyonaga A, Oho K, Sakai T, Tayama C, Masumoto H, et al. Portal-hypertensive gastropathy develops less in cirrhotic patients with fundal varices. J Hepatol. 1997;26:1235–41.
14. Tayama C, Iwao T, Oho K, Toyonaga A, Tanikawa K. Effect of large fundal varices on changes in gastric mucosal hemodynamics after endoscopic variceal ligation. Endoscopy. 1998;30:25–31.
15. Sarin SK, Mirsa SP, Singal A, Thorat V, Broor SL. Evaluation of the incidence and significance of the mosaic pattern in patients with cirrhosis, noncirrhotic portal fibrosis, and extrahepatic obstruction. Am J Gastroenterol. 1988;83:1235–9.
16. Spina GP, Arcidiacono R, Bosch J, Pagliaro L, Burroughs AK, Santambrogio R, et al. Gastric endoscopic features in portal hypertension: final report of a consensus conference, Milan Italy, September 19 1992. J Hepatol. 1994;21:461–7.
17. Toyonaga A, Iwao T, Shimotsuuru Y, Tanikawa K. Endoscopic histologic and haemodynamic studies on portal hypertensive gastric mucosa. J Gastroenterol Hepatol. 1989;4:132–5.
18. Hayashi S, Saeki T. Endoscopic diagnosis of PHG and GAVE. Jpn J Port Hypertens. 2007;13:112–6.
19. Papazian A, Braillon A, Dupas JL, Sevenet F, Capron JP. Portal hypertensive gastric mucosa: an endoscopic study. Gut. 1986;27:1199–203.
20. Cales P, Zabotto B, Meskens C, Caucanas JP, Vinel JP, Desmorat H. Gastroesophageal endoscopic features in cirrhosis: observer variability, interassociations, and relationship to hepatic dysfunction. Gastroenterology. 1990;98:156–62.
21. Primignani M, Carpinelli L, Preatoni P, Battaglia G, Carta A, Prada A. Natural history of portal hypertensive gastropathy in patients with liver cirrhosis. Gastroenterology. 2000;119:181–7.
22. Sarin SK, Shahi HM, Jain M, Jain AK, Issar SK, Murthy NS. The natural history of portal hypertensive gastropathy: influence of variceal eradication. Am J Gastroenterol. 2000;95:2888–93.
23. Naveau S, Bedossa P, Poynard T, Mory B, Chaput JC. Portal hypertensive colopathy. A new entity. Dig Dis Sci. 1991;36:1774–81.
24. DePalma GD, Rega M, Masone S, Persico F, Siciliano S, Patrone F, et al. Mucosal abnormalities of the small bowel in patients with cirrhosis and portal hypertension: a capsule endoscopy study. Gastrointest Endosc. 2005;62:529–34.
25. Kodama M, Uto H, Numata M, Hori T, Murayama T, Sasaki F, et al. Endoscopic characterization of the small bowel in patients with portal hypertension evaluated by double balloon endoscopy. J Gastroenterol. 2008;43:589–96.
26. Tam TN, Ng WW, Lee SD. Colonic mucosal changes in patients with liver cirrhosis. Gastrointest Endosc. 1995;42:408–12.
27. Ito K, Shiraki K, Sakai T, Yoshimura H, Nakano T. Portal hypertensive colopathy in patients with liver cirrhosis. World J Gastroenterol. 2005;1(1):3127–30.
28. Bini EJ, Lascarides CE, Micale PL, Weinshel EH. Mucosal abnormalities of the colon in patients with portal hypertension: an endoscopic study. Gastrointest Endosc. 2000;52:511–6.

29. Yamakado S, Kanazawa H, Kobayashi M. Portal hypertensive colopathy: endoscopic findings and the relation to portal pressure. Intern Med. 1995;34:153–7.
30. Diaz-Sanchez A, Nunez-Martinez O, Gonzalez-Asanza C, Matilla A, Merino B, Rincon D, et al. Portal hypertensive colopathy is associated with portal hypertension severity in cirrhotic patients. World J Gastroenterol. 2009;15:4781–7.
31. Guimaraes RAP, Perazzo H, Machado L, Terra C, Perez RM, Figueiredo FAF. Prevalence, variability, and outcomes in portal hypertensive colopathy: a study in patients with cirrhosis and paired controls. Gastrointest Endosc. 2015;82:469–76.
32. Chen LS, Lin HC, Lee FY, Hou MC, Lee SD. Portal hypertensive colopathy in patients with cirrhosis. Scand J Gastroenterol. 1996;31:490–4.
33. Misra SP, Dwivedi M, Misra V, Dharmani S, Kunwar BK, Arora JS. Colonic changes in patients with cirrhosis and in patients with extrahepatic portal vein obstruction. Endoscopy. 2005;37:454–9.
34. Higaki N, Matsui H, Imaoka H, Ikeda Y, Murakami H, Hiasa Y, et al. Characteristic endoscopic features of portal hypertensive enteropathy. J Gastroenterol. 2008;43:327–31.

Chapter 47
Treatment of Portal Hypertensive Gastroenteropathy

Kazuhiko Oho

Abstract Treatment of portal hypertensive gastropathy (PHG) essentially required reduction of portal blood pressure, for which drug therapy is recommended rather than other procedures. As PHG is a noninflammatory disease, sucralfate, H2 receptor antagonists, and proton pump inhibitors are ineffective, while propranolol is reported to be effective and has been used to reduce portal blood pressure in patients with PHG. On the other hand, the main differences of portal hypertensive colopathy and portal hypertensive enteropathy are vascular lesions, for which endoscopic treatment is the standard.

Keywords Portal hypertensive gastropathy · Portal hypertensive colopathy · Portal hypertensive enteropathy · Propranolol · Portosystemic shunt surgery · Transjugular intrahepatic portosystemic shunt · Argon plasma coagulation

47.1 Introduction

Treatment of portal hypertensive gastropathy (PHG), portal hypertensive colopathy (PHC), and portal hypertensive enteropathy (PHE) focuses on acute or chronic hemorrhage. As treatment of PHG essentially requires reduction in portal blood pressure, drug therapy is recommended rather than endoscopic treatment. On the other hand, the main differences of PHC and PHE are vascular lesions, for which endoscopic treatment and interventional radiology are also performed (Table 47.1).

K. Oho
Kurume University School of Medicine, Fukuoka, Japan

Department of Gastroenterology and Hepatology, Yanagawa Hospital, Fukuoka, Japan
e-mail: k-oho@yanagawa-hsp.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_47

Table 47.1 Options of treatment for PHG, PHC, and PHE

	PHG	PHC and PHE
Treatment	Iron replacement	Iron replacement
	Transfusion	Transfusion
	Portal pressure-reducing agents	Portal pressure-reducing agents
Salvage treatment	Portosystemic shunt surgery or TIPS	Portosystemic shunt surgery or TIPS
	APC	APC
		Sclerotherapy/ligation[a]
		Tissue adhesive injection therapy[a]
		B-RTO[a]

PHG portal hypertensive gastropathy, *PHC* portal hypertensive colopathy, *PHE* portal hypertensive enteropathy, *APC* argon plasma coagulation, *TIPS* transjugular intrahepatic portosystemic shunt, *B-RTO* balloon-occluded retrograde transvenous obliteration
[a]For ectopic varices

47.2 Treatment of PHG

Sucralfate, H2 receptor antagonists, and proton pump inhibitors are ineffective for PHG [1, 2]. Only drugs and techniques lowering portal blood pressure are effective.

47.2.1 Propranolol

Since Lebrec et al. [3] reported the effects of propranolol on PHG, its efficacy has been validated [4, 5]. Perez-Ayuso et al. [4] demonstrated a reduction in the rebleeding rate and improvement of the survival rate by propranolol in a double-blind study [6, 7]. Alleviation of gastric mucosal congestion as an effect of propranolol has also been observed. However, administration of the drug to patients with active bleeding from PHG may cause β1 receptor blockage-induced reduction in cardiac output, which must be monitored for [8].

47.2.2 Other Drug Therapies

Portal blood pressure-lowering action of vasopressin and somatostatin has also been reported. Alleviation of gastric mucosal congestion by vasopressin has been observed [9, 10], but it may promote intestinal oxygen consumption and reduce oxygen saturation in the gastric mucosa, impairing the mucosa, for which oxygen administration is recommended because it decreases the reduction in oxygen saturation [10]. Alleviation of gastric mucosal congestion by somatostatin has also been demonstrated [11]. Its influence on systemic circulatory dynamics is mild, and no adverse effects have been reported.

47.2.3 Portosystemic Shunt Surgery

Portosystemic shunt surgery is the most effective method to reduce portal blood pressure, and its effects on PHG have been frequently reported [12–14]. However, aggravation of liver function, development of hepatic encephalopathy by surgical shunt, and reduction of liver blood flow volume must be considered.

47.2.4 Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Portal blood pressure is reduced via a stent placed between the intrahepatic portal and hepatic veins using this treatment method [15]. A reduction in portal blood pressure similar to that obtained via a portosystemic shunt may be achieved, and it was reported to be effective against PHG [16]. Although it is less invasive than the portosystemic shunt surgery, strict follow-up to prevent stent occlusion and hepatic encephalopathy is necessary [17].

47.2.5 Argon Plasma Coagulation (APC)

Argon plasma coagulation (APC) method has been reported as a useful endoscopic treatment for the surface of the gastrointestinal mucosa, mainly for cases with the source of bleeding in the capillary blood vessels and venules. More rapid and continuous hemostasis can be achieved using APC compared with using a heater probe, which also stops bleeding by heat coagulation [18]. Effects on PHG and gastric antral vascular ectasia have been demonstrated in many studies [19, 20].

47.3 Treatment of PHC and PHE

In general, treatment to prevent PHC and PHE is not performed; however, hemorrhagic cases are treated. As these diseases are rare, clinical data are insufficient, and no standard guidelines are available for the treatment of symptomatic PHC or PHE. For bleeding from vascular lesions, endoscopic treatment, such as laser coagulation [21] and APC, has recently been selected for many cases. Balzer et al. [22] reported that TIPS was effective for bleeding from vascular lesions. Bleeding from rectal varices is treated with sclerotherapy or ligation in many cases [23]. For treatment of large varices in the small and large intestines, endoscopic embolization with tissue adhesives and balloon-occluded retrograde transvenous obliteration (B-RTO) [24], which is intervention radiology, have been reported to be effective [25, 26]. The efficacy of TIPS has also been frequently reported [27, 28].

Drugs with portal blood pressure-lowering action, such as propranolol and vasopressin, are expected to be effective, but no study evaluating the efficacy of drug therapy has been reported.

47.4 Summary

Many points remain unclear with regard to the pathologies of PHG, PHC, and PHE. Moreover, endoscopic findings are diverse, subsequently diversifying treatment. The standard treatment is reduction of portal blood pressure using drugs. For vascular lesions and varices, endoscopic and interventional radiology treatments may be effective.

References

1. McCormack TT, Sims J, Eyre-Brook I, Kennedy H, Goepel J, Johnson AG, et al. Gastric lesion in portal hypertension: inflammatory gastritis or congestive gastropathy? Gut. 1985;26:1226–32.
2. Quintero E, Pique JM, Bombi JA, Bordas JM, Sentis J, Elena M, et al. Gastric mucosal vascular ectasias causing bleeding in cirrhosis. A distinct entity associated with hypergastrinemia and low serum levels of pepsinogenI. Gastroenterology. 1987;93:1054–61.
3. Lebrec D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis. N Engl J Med. 1981;305:1371–4.
4. Perez-Ayuso RM, Pique JM, Bosch J, Panes J, Gonzales A, Perez R, et al. Propranolol in prevention of recurrent bleeding from severe portal hypertensive gastropathy in cirrhosis. Lancet. 1991;337:1431–4.
5. Sarin SK, Shahi HM, Jain M, Jain AK, Issar SK, Murthy NS. The natural history of portal hypertensive gastropathy: influence of variceal eradication. Am J Gastroenterol. 2000;95:2888–93.
6. Panes J, Bordas JM, Pique JM, Garcia-Pagan JC, Feu F, Teres J, et al. Effects of propranolol on gastric mucosal perfusion in cirrhotic patients with portal hypertensive gastropathy. Hepatology. 1993;17:213–8.
7. Shigemori H, Iwao T, Ikegami M, Toyonaga A, Tanikawa K. Effects of propranolol on gastric mucosal perfusion and serum gastrin level in cirrhotic patients with portal hypertensive gastropathy. Dig Dis Sci. 1994;39:2433–8.
8. Burroughts AK, Jenkins WJ, Sherlock S, Dunk A, Walt RP, Osuafor TO, et al. Controlled trial of propranolol for the prevention of recurrent variceal haemorrhage in patients with cirrhosis. N Engl J Med. 1983;309:1539–42.
9. Panes J, Pique JM, Bordas JM, Llach J, Bosch J, Teres J, et al. Reduction of gastric hyperemia by glypressin and vasopressin administration in cirrhotic patients with portal hypertensive gastropathy. Hepatology. 1994;19:55–60.
10. Iwao T, Toyonaga A, Shigemori H, Oho K, Sumino M, Sato M, et al. Vasopressin plus oxygen vs vasopressin alone in cirrhotic patients with portal-hypertensive gastropathy: effects of gastric mucosal perfusion and oxygenation. J Gastenterol Hepatol. 1996;11:216–22.
11. Panes J, Pique JM, Bordas JM, Casadevall M, Teres J, et al. Effect of bolus injection and continuous infusion of somatostatin on gastric perfusion in cirrhotic patients with portal hypertensive gastropathy. Hepatology. 1994;20:336–41.

12. Sarfeh IJ, Juler GL, Stemmer EA, Mason GR. Results of surgical management of haemorrhagic gastritis in patients with gastroesophageal varices. Surg Gynecol Obstet. 1982;155:167–70.
13. Resnick RH, Iber FL, Ishihara AM, Chalmers TC, Zimmerman H. A controlled study of the therapeutic portacaval shunt. Gastroenterology. 1974;67:843–57.
14. Rueff B, Prandi D, Degos F, Sicot J, Degos JD, Sicot C, et al. A controlled study of therapeutic portacaval shunt in cirrhosis. Lancet. 1976;1:655–9.
15. Rosch J, Hanafee WN, Snow H. Work in progress. Transjugular portal venography and radiologic portacaval shunt: an experimental study. Radiology. 1969;92:1112–4.
16. Patrick SK, Marco L, David AA. Gastric mucosal responses to intrahepatic portosystemic shunting in patients with cirrhosis. Gastroenterology. 2000;118:905–11.
17. Ong JP, Sands M, Younossi ZM. Transjugular intrahepatic portosystemic shunts (TIPS). J Clin Gastroenterol. 2000;30:14–28.
18. Cipolletta L, Bianco MA, Rotondano G, Piscopo R, Prisco A, Garofano ML. Prospective comparison of argon plasma coagulator and heater probe in the endoscopic treatment of major peptic ulcer bleeding. Gastrointest Endosc. 1998;48:191–5.
19. Galcia N, Sanyal AJ. Portal hypertensive gastropathy and gastric antral vascular ectasia. Curr Treat Options Gastroenterol. 2001;4:163–71.
20. Ripoll C, Garcia-Tsao G. Treatment of gastropathy and gastric antral vascular ectasia in patients with portal hypertension. Curr Treat Options Gastroenterol. 2007;10:483–94.
21. Naveau S, Aubert A, Poynard T, Chaput JC. Long-term results of treatment of vascular malformations of the gastrointestinal tract by neodymium-YAG laser photocoagulation. Dig Dis Sci. 1990;35:821–6.
22. Balzer C, Lotterer E, Kleber G, Fleig WE. Transjugular intrahepatic portosystemic shunt for bleeding angiodysplasia-like lesions in portal-hypertensive colopathy. Gastroenterology. 1998;115:167–72.
23. Johansen K, Bardin J, Orloff MJ. Massive bleeding from hemorrhoidal varices in portal hypertension. JAMA. 1980;224:2084–5.
24. Kanagawa H, Mima S, Kouyama H, Gotoh K, Uchida T, Okuda K. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. J Gastroenterol Hepatol. 1996;11:51–8.
25. Chen WC, Hou MC, Lin HC, Chang FY, Lee SD. An endoscopic injection with N-butyl-2-cyanoacrylate used for colonic variceal bleeding: a case report and review of the literature. Am J Gastroenterol. 2000;95:540–2.
26. Haruta I, Isobe Y, Ueno E, Toda J, Mitsunaga A, Noguchi S, et al. Balloon-occluded retrograde transvenous obliteration (BRTO), a promising nonsurgical therapy for ectopic varices: a case report of successful treatment of duodenal varices by BRTO. Am J Gastroenterol. 1996;91:2594–7.
27. Katz JA, Bubin RA, Cope C, Holland G, Brass CA. Recurrent bleeding from anorectal varices: successful treatment with a transjugular intrahepatic portosystemic shunt. Am J Gastroenterol. 1993;88:1104–7.
28. Fantin AC, Zala G, Risti B, Debatin JF, Schöpke W, Meyenberger C. Bleeding anorectal varices: successful treatment with a transjugular intrahepatic portosystemic shunting. Gut. 1996;38:932–5.

Part V
Complications of Portal Hypertension: Portal Vein Thrombosis

Chapter 48
Diagnosis of Portal Vein Thrombosis

Shigehiro Kokubu

Abstract Portal vein thrombosis is considered to develop from portal venous vascular wall disorder, abnormal portal venous flow, and abnormalities of the blood coagulation system as the thrombogenic origins. Portal vein thrombosis can easily occur in patients with hepatic cirrhosis due to three additional factors. The first factor is the hyperpermeability of the gastrointestinal mucous membrane. Cirrhosis creates an environment susceptible to bacterial translocation, and loads to the flow of lipopolysaccharide into a portal vein, resulting in sinusoid wall injury. The second factor is clot formation promoted by portal venous congestion (sluggish blood flow) due to portal hypertension. The third factor is a decrease of antithrombin-III synthesis in liver cirrhosis. Among the underlying diseases of 539 cases of portal vein thrombosis in Japan in 2014, there were 434 cases (80.5%) of portal hypertension, whose breakdown consisted of 406 cases (75.3%) of liver cirrhosis, 25 cases of idiopathic portal hypertension, 8 cases of extrahepatic obstruction, and 7 cases of others, while 105 cases (19.5%) were not associated with portal hypertension. Secondary portal vein thrombus accounted for 69 (12.8%) of the total, if it is defined as that developed within 30 days after an operation or interventional radiology.

Keywords Etiology of portal thrombus · Liver cirrhosis · Protein C · Protein S
Secondary portal thrombus

48.1 Onset-Related Factor of the Portal Vein Thrombosis

Portal vein thrombosis is a disease, whereby clot formation occurs in the portal system due to multifactorial causes. It has a wide range of presentation, ranging from an incidental finding in an asymptomatic patient to symptoms of exacerbated portal

S. Kokubu
Shin-yurigaoka General Hospital Institute for Liver Disease Minimal Invasive Treatment center, Endoscopic Center, Kawasaki, Kanagawa, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_48

hypertension, intestinal tract necrosis, shock, and liver failure, depending on the patient's underlying disease and its time of onset. Therefore, it is important to consider the underlying disease and its onset in the context of treatment and management.

48.2 Etiology and Epidemiology of Portal Vein Thrombosis

48.2.1 Cause

Generally, portal vein thrombosis is thought to develop by the following three abnormalities: portal venous vascular wall disorder, abnormal portal venous flow, and abnormalities of the blood coagulation system (Virchow's triad) as the thrombogenic origin. The causes include cirrhosis, blood clotting gene abnormality, a myeloproliferative disease, extension of a local inflammatory response, cancer progression, and consequence of abdominal surgery. Although it is not found in Japanese, hereditary factors such as factor V Leiden variation or 20,210 prothrombotic gene variation are found to contribute to portal vein thrombosis formation in Europe and America [1].

In addition to the general factors mentioned above, a background where portal vein thrombosis can easily occur is hepatic cirrhosis due to the three additional factors. The first factor is the hyperpermeability of the gastrointestinal mucous membrane.

Cirrhosis creates an environment susceptible to bacterial translocation, and loads to the flow of lipopolysaccharide (LPS) into a portal vein, resulting in the sinusoid wall injury. The second factor is clot formation in the blood vessel promoted by portal venous congestion (sluggish blood flow) due to portal hypertension. This mechanism has been considered as the main cause of portal vein clot in Europe and America, but in Japan the research group of the Ministry of Health, Labour and Welfare headed by Professor Okuda and Professor Okudaira could not confirm it as the primary factor. The third factor is a decrease of antithrombin-III (AT-III) synthesis in liver cirrhosis. AT III, which is known as a heparin cofactor, gradually decreases as cirrhosis progresses. A portal vein clot can be formed when another causative factor joins.

48.2.2 Frequency

Portal vein thrombosis is most often associated with cirrhosis in adults. The incidence of portal vein thrombosis is related to the severity of cirrhosis. It has been reported that portal vein thrombosis was found in less than 1% of the patient with compensated cirrhosis [2] but in 8–25% of the patients who are waiting for a liver transplantation [3]. Although the frequency of portal vein thrombus complications, as seen from the total number of patients, is unknown as a whole, 79 patients

(11.2%) of 701 cirrhotic patients admitted to the hospital during 4 years had portal vein thrombosis, of which 45 were symptomatic (57%) and 34 were asymptomatic (43%) portal vein thrombosis. Thirty-one of the 79 patients (39%) were found to have gastrointestinal bleeding, 18 were reported to have ruptured esophagogastric varices, and 13 had portal hypertensive gastropathy [4]. Moreover, congenital gene deficiency, related to protein C and protein S, has frequently been pointed out as the bleeding/coagulation factor, and even though their frequency is not high in Japan, there are a few reports on them. On the other hand, there are quite a few cases in which both protein S and protein C, or either one of them, have decreased, according to the measurement carried out after portal vein thrombus was observed.

In Japan, a nationwide survey was performed to clarify the present situation of the portal vein thrombosis with regard to frequency, diagnosis, and treatment, which was conducted by the Society of Portal Hypertension in 2014 [5]. According to the results in 539 cases of portal vein thrombosis, the underlying cause was portal hypertension related diseases in 434 cases (80.5%), of which the overwhelming number, 406 cases (75.3%) were associated with liver cirrhosis, and the remainder were due to other causes led by IPH, EHO and others. Disease unassociated with portal hypertension, including biliary tract diseases, malignant tumors, pancreatic diseases and other causes, accounted for in 105 cases (19.5%).

48.3 Diagnosis of the Portal Vein Thrombosis

Diagnosis of a portal vein thrombosis is not difficult with recent advances in imaging techniques. It is depicted as isoechoic or hyperechoic structure by comparison with the intraluminal section of portal vein by abdominal B-mode ultrasonography. A fresh clot is depicted as an isoechoic structure, and an old clot is depicted as a hyperechoic structure similar to a fibrin lump formation [6]. In addition, color dopula ultrasonography [7] and positive intra-thrombus enhancement on contrast-enhanced ultrasonography are effective for the diagnosis of portal thrombus [8, 9].

A coronal image can be built by the techniques of minimum intensity projection (MIP) and multiplanner reconstruction (MPR), as well as an axial image by the examination of contrast-enhanced abdominal CT, and the clot is depicted as a low-density foci in the blood vessels. This enables grasping the hemodynamics of the collateral circulation which includes a more thrombotic expanse and at the same time esophagogastric varices. A fresh clot may be depicted by plain CT as a high-density lesion [10].

D-dimer and FDP are useful blood tests in coaglatin system, and an abnormal high level suggests an acute clot formation. However, high levels are observed in patient with ascites, and careful interpretation of the results is necessary. In addition, further investigation is necessary to clarify the causative blood clotting abnormality when portal vein thrombosis is diagnosed for the first time.

References

1. DeLeve LD, Valla DC, Garcia-Tsao G. Vascular disorders of the liver. Hepatology. 2009;49:1729–64.
2. Okuda K, Ohnishi K, Kimura K, Matsutani S, Sumida M, Goto N, et al. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. Gastroenterology. 1985;89:279–86.
3. Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut. 2005;54:691–7.
4. Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40:736–41.
5. Kojima S, Watanabe N, Matsutani S, Oho K, Ohta M, Koizumi J, Kokubu S, et al. Current status of portal vein thrombosis in Japan: the results of the questionnaire survey. J JSPH. 2016;22(2):176–89.
6. Okuwaki Y, Kokubu S. In: Japan Society of Portal Hypertension, editors. Portal vein thrombosis: clinical manual of portal hypertension. Tokyo: Nankodo; 2015.
7. Tessler FN, Gehring BJ, Gomes AS, Perrella RR, Ragavendra N, Busuttil RW, et al. Diagnosis of portal vein thrombosis: value of color Doppler imaging. AJR Am J Roentgenol. 1991;157:293–6.
8. Rossi S, Rosa L, Ravetta V. Contrast-enhanced versus conventional and color Doppler sonography for the detection of thrombosis of the portal and hepatic venous system. AJR Am J Roentgenol. 2006;186:763–73.
9. Maruyama H, Takahashi M, Shimada T, Yokosuka O. Emergency anticoagulation treatment for cirrhosis patients with portal vein thrombosis and acute variceal bleeding. Scand J Gastroenterol. 2012;47(6):686–91.
10. Parvey HR, Raval B, Sandler CM. Portal vein thrombosis: imaging findings. AJR Am J Roentgenol. 1994;162:77–81.

Chapter 49
Treatment of the Portal Vein Thrombosis

Shigehiro Kokubu

Abstract The treatment of portal vein thrombosis is performed based on a symptomatic acute clot or an asymptomatic chronic clot and further depends on whether the underlying disease is cirrhosis or not. In all cirrhotic cases, attention should be paid to hemorrhagic complications. In particular, it is necessary to perform appropriate prophylactic endoscopic injection sclerotherapy/endoscopic variceal ligation in complicated case of esophagogastric varices. In recent years the use of antithrombin-III (AT-III) preparations and danaparoid sodium have increased in place of heparin, urokinase, and warfarin for the treatment of portal vein thrombosis. Based on the fact that antithrombotic action (fibrinolysis) has been reported even with AT-III alone, and that AT-III doesn't affect the bleeding tendency, it is safe and effective to use it for portal vein thrombosis with esophagogastric varices. And danaparoid sodium has higher anti-factor Xa activity than heparin. In addition, the usefulness of danaparoid with less risk of bleeding has also been reported.

Keywords AT-III preparations · Danaparoid sodium · Hemorrhagic complications · D-dimer · FDP

49.1 Treatment of Portal Vein Thrombosis: Present Situation

The treatment of portal vein thrombosis is performed based on a symptomatic acute clot or an asymptomatic chronic clot and further depends on whether the underlying disease is cirrhosis or not. Anticoagulation therapy using heparin and warfarin and thrombolytic therapy using urokinase and tissue plasminogen activator (t-PA) were common conventional treatments, but in recent years, the use of antithrombin-III (AT-III) preparations and danaparoid sodium has increased.

S. Kokubu (✉)
Shin-yurigaoka General Hospital Institute for Liver Disease Minimal Invasive Treatment, Endoscopic Center, Kawasaki, Kanagawa, Japan

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_49

49.2 Non-cirrhotic Disease

Thrombolysis using prompt anticoagulant therapy or catheter is carried out for acute portal vein thrombosis in patients without cirrhosis. If there are coexistent esophagogastric varices in patient with chronic portal vein thrombosis where collaterals have developed, the so-called extrahepatic portal vein obstruction, a standard conventional treatment of esophagogastric varices, is considered [1].

Long-term anticoagulant therapy for non-cirrhotic chronic portal vein thrombosis should be considered when constant blood-clotting abnormality on the basis has been observed, and it is not considered to be cirrhosis of the liver. Anticoagulant therapy should start after applying preventive treatment in the case of concomitant esophagogastric varices. For acute portal vein thrombosis, a catheter is inserted from the portal vein or transjugular intrahepatic portosystemic shunting route to directly remove the thrombus. Direct dissolution therapy is often tried on the spot. The consensus on non-cirrhotic portal vein thrombosis and the recent American Association for the Study of Liver Diseases (AASLD) practice guidelines on liver vascular disorders advocate anticoagulation in acute portal vein thrombosis, as recanalization may occur in up to 80% of cases [2].

49.3 Cirrhotic Disease

With regard to cirrhosis of the liver, on the other hand, there is at present no standard treatment in so far as its method, the timing of starting treatment, and its indication are concerned for portal vein thrombosis in cirrhosis cases, regardless of whether acute or chronic [3]. The reason for this is that in liver cirrhosis cases, in addition to bleeding tendency due to reductions in platelets and coagulation factors, patients often have esophagogastric varices and portal hypertensive gastroenteropathy [4], which induces a high risk of bleeding, as well as a concern over the possibility of triggering bleeding, due to anticoagulation therapy, contrary to expectation [5]. In addition, there are cases in which portal vein thrombosis spontaneously disappeared (20–30%), as well as asymptomatic cases.

Anticoagulation therapy with heparin and warfarin is common as a treatment method, but in all cases, attention should be paid to hemorrhagic complications. In particular, it is necessary to perform appropriate prophylactic endoscopic injection sclerotherapy (EIS)/endoscopic variceal ligation (EVL) in complicated esophagogastric varices cases. The efficacy and safety of anticoagulant therapy with low-molecular-weight heparin were recently reported in cirrhotic patients with portal vein thrombosis, while a few adverse events were also reported, such as hemorrhagic complications and heparin-induced thrombocytopenia [6].

In Japan, based on the viewpoint that portal vein thrombosis, accompanied by cirrhosis, often involves a decrease in AT-III and contributes to hypercoagulation, AT-III supplementation therapy has been carried out as an antithrombotic therapy [7].

Based on the fact that antithrombotic action (fibrinolysis) has been reported even with AT-III alone [8], and that AT-III doesn't affect bleeding tendency, it is safe and effective to use it for portal vein thrombosis with esophagogastric varices. In addition, AT-III administration has an advantage from a safety and efficacy point of view for portal vein thrombus after splenectomy [9, 10] and pre- and post-liver transplantation [11].

In addition, the usefulness of danaparoid with less risk of bleeding has been reported during the past 10 years [12–14]. Danaparoid, a low-molecular -weight heparinoid, mainly composed of heparan sulfate and derived from the mucosa of the small intestine of swine, has higher anti-Xa activity than heparin or low-molecular-weight heparin, and is less likely to cause bleeding. In our examination of 48 cases in which portal vein thrombus was treated with AT-III and danaparoid, and evaluated before and after treatment, the effective rate, combined with thrombus disappearance and reduction, was 83.3% (Table 49.1, Fig. 49.1). Moreover, no adverse hemorrhagic occurrence was observed. In the determination of its therapeutic effect, D-dimer and fibrin/fibrinogen degradation products (FDP) mentioned in Chapter. 48 (see Sect. 48.3) were the optimal indicators (Fig. 49.2).

49.4 Future Developments

Most of the treatment issues of portal vein thrombosis, particularly in cases of cirrhosis of the liver, have remained unresolved, due to the scarcity of evidence in terms of treatment adaptability, selection of therapeutic drugs, the timing for its start, treatment duration, etc. However, from October 2014 through to March 2016, a prospective randomized controlled trial of the portal vein thrombosis using the world's first AT-III formulation was carried out in Japan [15]. According to the results, the proportion of patients with complete response or partial response to portal vein thrombosis was significantly higher in the AT-III group (55.6%; 20/36 patients; 95% confidence interval, 38.1-72.1) than in the placebo group (19.4%; 7/36 patients; 95% confidence interval, 8.2-36.0) (p=0.003). At that time the frequency of cases

Table 49.1 Therapeutic effect of AT-III with danaparoid sodium in treatment of portal vein thrombosis

	N	Disappear	Decrease	No change	Adverse event
AT-III	20	8	7	5	0
AT-III + danaparoid	28	11	14	3	0
Total	48	19 (39.5%)	21 (43.8%)	8 (16.7%)	0

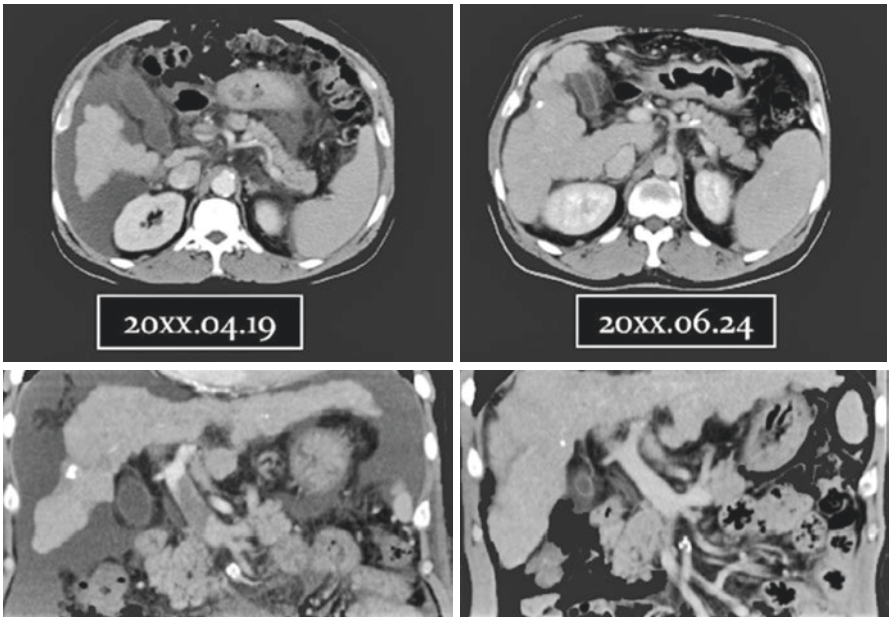


Fig. 49.1 Imaging of portal vein thrombosis using multi-detector computed tomography (MD-CT) (upper, axial view; lower, coronal view)

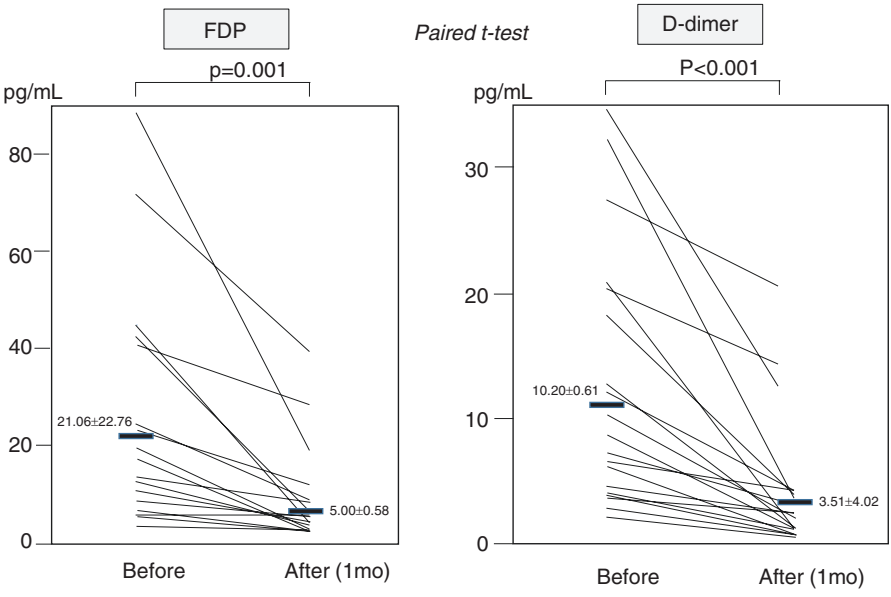


Fig. 49.2 Change of D-dimer and FDP: before and after administration of danaparoid sodium with AT-III in portal vein thrombosis. Both FDP and D-dimer significantly decreased after the administration of danaparoid Na with AT-III ($n = 47$)

in which thrombus spontaneously disappeared was also revealed. Further details of objective data will be reported later. Given this situation, further clinical research is needed in the future, including meeting the challenge of conducting a trial of danaparoid sodium which is the next treatment method and that of direct oral anticoagulant (DOAC) which is a new oral preparation.

References

1. DeLeve LD, Valla DC, Garcia-Tsao G, American Association for the Study liver Disease. Vascular disorders of the liver. Hepatology. 2009;49:1729–64.
2. Tsochatzis EA, et al. Systematic review: portal vein thrombosis in cirrhosis. Aliment Pharmacol Ther. 2010;31:336–74.
3. Valla DC. Thrombosis and anticoagulation in liver disease. Hepatology. 2008;47:1384–93.
4. Amitrano L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40:736–41.
5. Delgado MG, Seijo S, Yepes I, et al. Efficacy and safety of anticoagulation on patient with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol. 2012;10:776–83.
6. Amitrano L, Guardascione MA, Menchise A, Martino R, Scaglione M, Giovine S, et al. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. J Clin Gastroenterol. 2010;44:448–51.
7. Takada M, Kokubu S. Clinical pathophysiology and treatment of portal hypertension. TreatmentUpdate. 1999;81:235–42.
8. Schpper HG, Ten JW. Antithrombin III transfusion in patient with hepatic cirrhosis. Br J Haematol. 1982;52:25–33.
9. Kawanaka H, Akahoshi T, Kinjo N, et al. Impact of antithrombin III concentrates on portal vein thrombus after splenectomy in patients with liver cirrhosis and hypersplenism. Ann Surg. 2010;251:76–83.
10. Kawanaka H, Akahoshi T, Itoh S, et al. Optimizing risk stratification in portal vein thrombus after splenectomy and prophylaxis with antithrombin III concentrates and danaparoid sodium in liver cirrhosis with portal hypertension. J Am Coll Surg. 2014;219:865–74.
11. John BV, Konjeti R, Aggarwal A, et al. Impact of untreated portal vein thrombosis on pre and post liver transplant outcomes in cirrhosis. Ann Hepatol. 2013;12:952–8.
12. Shuto T, Yazaki Y, Sugawara K. In use experience of danaparoid sodium for the portal vein thrombosis. J Japan Portal Hypertens. 2005;11(2):171–3.
13. Kokubu S. Diagnosis, pathogenesis and latest therapy in portal hypertension. J Japan Gastroenterol. 2008;105:1588–96.
14. Naeshiro N, Aikata H, Chayama K, et al. Efficacy and safety of the anticoagulant drug, danaparoid sodium, in the treatment of portal vein thrombus in patient with liver cirrhosis. Hepatorol Res. 2015;45:656–62.
15. Hidaka H, Kokubu S, Satou T, Katsushima S, et al. Antithrombin III administration for portal vein thrombosis in patient with liver disease; a randomized double blind controlled trial. Hepatol Res. 2018;48(3):E107–16. https://doi.org/10.1111/hepr.12934.

Part VI
Complications of Portal Hypertension: Refractory Ascites

Chapter 50
Diagnosis of Refractory Ascites

Makoto Segawa and Isao Sakaida

Abstract Refractory ascites is a complication of decompensated liver cirrhosis and is an indicator of poor prognosis. Portal hypertension and renal sodium retention are involved in the occurrence of refractory ascites. The diagnosis of refractory ascites is based on the criteria advocated by the International Ascites Club (IAC). Exclusion of the conditions that induce transient refractoriness to diuretics is important in the differential diagnosis. In Japan, tolvaptan, an oral arginine vasopressin V_2 receptor antagonist, has been used as a new diuretic for ascites in combination with conventional diuretics since the drug was approved in 2013. As the relation between renal dysfunction and poor prognosis has become evident, preservation of renal function should be considered while selecting therapeutic options. An appropriate combination of diuretic therapy using tolvaptan and conventional diuretics may offer the possibility to control ascites without deterioration of renal function. Further investigation to clarify the role of the novel diuretic drug, tolvaptan, in the treatment of cirrhotic refractory ascites is necessary.

Keywords Refractory ascites · Mechanism · Diagnostic criteria · Arginine vasopressin V_2 receptor antagonist · Tolvaptan

50.1 Introduction

Ascites is a common major complication of liver cirrhosis. The risk of developing ascites within 10 years is >60% if the patient is not appropriately treated [1]. In most cases, ascites can be controlled by dietary sodium restriction and administration of diuretics. However, in 5–10% of patients, ascites gradually becomes resistant to

M. Segawa
Department of Kampo Medicine, Yamaguchi University Hospital, Ube, Yamaguchi, Japan

I. Sakaida (✉)
Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan
e-mail: sakaida@yamaguchi-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_50

treatment and is called refractory ascites. Refractory ascites is frequently associated with hepatorenal syndrome, spontaneous bacterial peritonitis, dilutional hyponatremia, muscle wasting, and pleural effusion. Refractory ascites is an indicator of poor prognosis, with a 2-year survival rate of approximately 30% [2]. Therefore, in cases of refractory ascites, appropriate therapeutic strategies, including liver transplantation, should be considered.

In the past, for the treatment of refractory ascites, a large volume of furosemide was used, which has often caused renal dysfunction. However, the relation between renal dysfunction and prognosis has recently become evident, and the value of renal protection during therapy is emphasized [3]. In 2015, the International Ascites Club (IAC) proposed new diagnostic criteria for acute kidney injury in patients with cirrhosis and recommended appropriate treatment according to clinical stage of acute kidney injury [4]. The key point in the management of refractory ascites is to diagnose the clinical stage of cirrhosis precisely and to initiate appropriate treatment without causing deterioration in renal function, thereby improving the patient's quality of life (QOL) and prognosis.

50.2 Mechanism of Formation of Refractory Ascites

The main factors contributing to the development of cirrhotic ascites are portal hypertension and renal sodium retention [5] (Fig. 50.1). Portal hypertension is induced by increased sinusoidal vascular resistance and increased portal flow volume. Sinusoidal vascular resistance is caused by architectural distortion because of liver fibrosis, and high sinusoidal vascular tone resulting from the increased local production of vasoconstrictors, such as angiotensin, endothelin, leukotrienes, and thromboxane, which is related to endothelial cell dysfunction [6]. Portal hypertension leads to the formation of collateral circulation and production of ascitic fluid. Hypoalbuminemia, because of hepatocyte dysfunction, causes decreased plasma osmotic pressure and leads to the production of transudative ascitic fluid.

In the systemic and splanchnic circulation, vasodilators such as nitric oxide, calcitonin gene-related peptide, substance P, carbon monoxide, and endogenous cannabinoids are overproduced, and vasodilation is induced. Sepsis is frequently associated with this process. Endothelial stretching and bacterial translocation are responsible for the local overproduction of vasodilators and other cytokines [7]. Hyperpermeability of the intestinal mucosa is often observed in patients with cirrhotic ascites, which results in bacterial translocation [8].

Arteriolar vasodilatation and pooling of blood in the splanchnic circulation cause a decrease in effective circulating volume. This change activates both the renin–angiotensin–aldosterone system and the sympathetic nervous system, which leads to renal sodium retention. The antidiuretic hormone vasopressin is also activated,

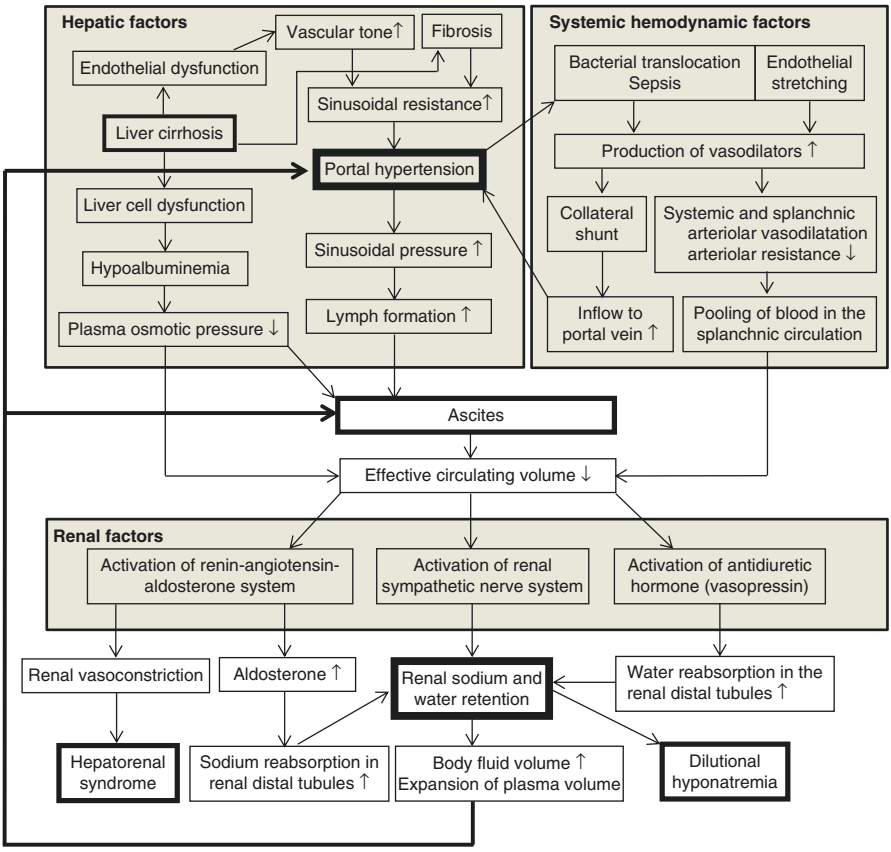


Fig. 50.1 Pathophysiology of cirrhosis and ascites formation

and dilutional hyponatremia is induced from reabsorption of the water in the renal distal tubules. As cirrhosis develops, effective circulating volume is further decreased, which causes a hepatorenal syndrome as a result of both severe renal vasoconstriction and a decrease in glomerular filtration rate.

These changes induce a continuous escape of fluid from the sinusoid or the splanchnic capillaries into the interstitial space. Although the shift of fluid is compensated by increased lymphatic drainage initially, as cirrhosis develops, the escape of fluid overwhelms the lymphatic return, and fluid finally accumulates in the peritoneal cavity. Moreover, when several factors, such as further activation of renal sodium and water reabsorption, impaired response to vasoconstrictors in the sinusoids, increased hydrostatic pressure in the peritoneal cavity, and diuretic-related complications, are involved, ascites becomes refractory to pharmacological intervention [9].

50.3 Diagnosis of Refractory Ascites

The diagnostic algorithm for refractory ascites to exclude other causes is shown in Fig. 50.2. Unresponsiveness to diuretics develops because of advanced cirrhosis or hemodynamic changes in the splanchnic and systemic circulations. Conversely, overadministration of diuretics directly induces acute kidney injury, which leads to refractoriness. Refractory ascites is diagnosed after excluding potential causes of uncontrolled ascites (e.g., peritoneal carcinomatosis, nephrogenic ascites, and hepatic vein thrombosis) and conditions that induce transient refractoriness (e.g., overuse of diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and nephrotoxic drugs such as aminoglycosides and noncompliance to diet and medications) [5].

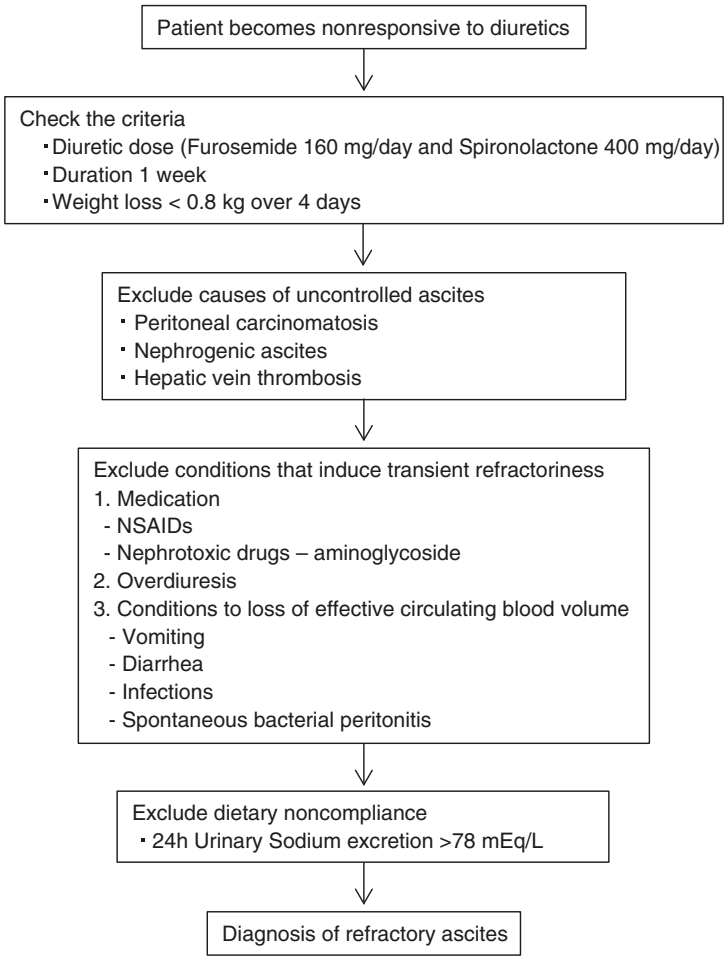


Fig. 50.2 Diagnostic algorithm for refractory ascites

Administration of NSAIDs impairs renal function by inhibiting the synthesis of vasodilating prostaglandins. Loss of effective circulating blood volume from vomiting, diarrhea, bleeding, bacterial infections, or spontaneous bacterial peritonitis induces renal failure. In these cases, medical management, such as discontinuation of the offending drug, resolution of the complication, and appropriate plasma volume expansion, will restore responsiveness to treatment.

Noncompliance with diet and medication is an important condition that needs to be ruled out in patients with poorly controlled ascites. Dietary compliance can be assessed accurately by 24-hour urinary sodium excretion [9]. Patients who gain weight despite excreting >78 mEq of sodium/day are not compliant with diet. First-line treatment of patients with cirrhosis and ascites consists of restriction of sodium to 88 mmoL/day (2000 mg/day) and diuretics. The value of 78 mEq of sodium/day is derived from the difference between sodium intake (2 mg/day = 88 mEq/day) and nonurinary loss (10 mEq/day) [10]. Completeness of collection can be assessed by measurement of urinary creatinine. Urinary creatinine excretion/day should be >15 mg of creatinine/kg (body weight) for men and >10 mg/kg for women [11].

50.4 Definition and Diagnostic Criteria of Refractory Ascites

In 1996 the IAC defined refractory ascites as "ascites that cannot be mobilized or early recurrence of ascites which cannot be satisfactorily prevented by medical therapy." It includes two subtypes: diuretic-resistant ascites and diuretic-intractable ascites [12] (Table 50.1). The diagnostic criteria were revised in 2003 [13] (Table 50.2). Diagnosis of refractory ascites is performed according to these criteria.

When we use these criteria in Japan, it is necessary to be careful with regard to some points. First, the described dose of diuretics is too high for most Japanese patients, because the average body size of Japanese is smaller than that of Europeans. In Japan, the standard maximum dose of diuretics is 100 mg/day for spironolactone and 80 mg/day for furosemide [14]. Second, the description of tolvaptan, an oral arginine vasopressin (AVP) V_2 receptor antagonist, is not included in the criteria. In Japan, tolvaptan was approved in 2013 as a drug for cirrhotic patients with edema.

Table 50.1 Definition of refractory ascites [12]

Refractory ascites: ascites that cannot be mobilized or the early recurrence of which (i.e., after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy. It can be divided into:
1. Diuretic-resistant ascites: ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to dietary sodium restriction and intensive diuretic treatment
2. Diuretic-intractable ascites: ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage

Table 50.2 Revised diagnostic criteria of refractory ascites [13]

1. Treatment duration: Patients must be on intensive diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 week and on a salt-restricted diet of <90 mmol or 5.2 g of salt/day
2. Lack of response: Mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake
3. Early ascites recurrence: Reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization
4. Diuretic-induced complications:
(a) Diuretic-induced hepatic encephalopathy is the development of encephalopathy in the absence of any other precipitating factor
(b) Diuretic-induced renal impairment is an increase of serum creatinine by >100% to a value >2 mg/dL in patients with ascites responding to treatment
(c) Diuretic-induced hyponatremia is defined as a decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L
(d) Diuretic-induced hypo- or hyperkalemia is defined as a change in serum potassium to <3 or >6 mmol/L despite appropriate measures

Since then, tolvaptan has been used as the standard diuretic for refractory ascites in combination with conventional diuretics [14]. However, in Europe and the United States, vaptans are not approved as therapeutic drugs for ascites [13–16].

50.5 Therapeutic Algorithm for Refractory Ascites in Japan

In 2015, the therapeutic algorithm for cirrhotic ascites was proposed in the revised Japanese clinical guidelines for liver cirrhosis [14]. In this algorithm, the recent standard therapeutic strategy for refractory ascites is described (Fig. 50.3). For a small to moderate amount of ascites, the first-choice diuretic is spironolactone (25–100 mg/day), and if it is not effective, furosemide (20–80 mg/day orally) is added. For a massive or nonresponsive ascites, under sodium restriction (5–7 g/day), either add-on therapy with tolvaptan (3.75–7.5 mg/day orally) or intravenous infusion of potassium canrenoate/furosemide is recommended. For those with severe hypoalbuminemia (albumin level below 2.5 g/dL), albumin infusion (20–25% albumin at 50 mL/day, up to six times per month) can be considered. For patients resistant to these medications, therapeutic large-volume paracentesis with albumin infusion or cell-free and concentrated ascites reinfusion therapy (CART) is indicated. If this therapy is not effective, peritoneovenous shunt (Denver shunt) or transjugular intrahepatic portosystemic stent-shunt (TIPS) is indicated. If this therapy also fails, liver transplantation should be considered.

In Japan, AVP V_2 receptor antagonist, which is not approved in Europe and the United States, is used as a standard drug for ascites. This discrepancy is because of varying results of clinical trials. An analysis of all-cause mortality up to 52 weeks reveals that satavaptan in combination with conventional diuretics has a negative

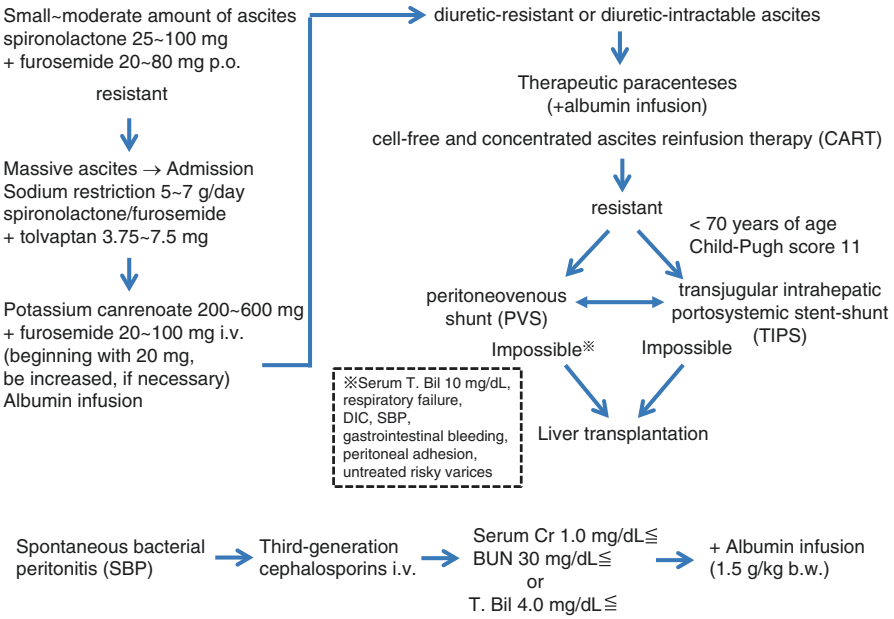


Fig. 50.3 Therapeutic algorithm for cirrhotic ascites [14]

effect compared with the placebo group in the prevention of recurrent ascites after large-volume paracentesis [15]. Serious side effects were not reported in short-term clinical trials of tolvaptan [16]. From this result, a small volume of tolvaptan in short-term use is considered to be a safe and effective therapeutic option for the control of ascites in Japan.

An appropriate combination of diuretic therapy using tolvaptan and conventional diuretics may have the possibility to control ascites without the deterioration of renal function.

Further investigation is necessary to clarify the role of the novel diuretic drug tolvaptan, in the treatment of cirrhotic refractory ascites.

References

1. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 188 studies. J Hepatol. 2006;44(1):217–31.
2. Gine's P, C'ardenas A, Arroyo V, et al. Management of cirrhosis and ascites. N Engl J Med. 2004;350:1646–54.
3. Tsien CD, Rabie R, Wong F. Acute kidney injury in decompensated cirrhosis. Gut. 2013;62(1):131–7.
4. Angeli P, Gin's P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol. 2015;62(4):968–74.

5. Salerno F, Guevara M, Bernardi M, et al. Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis. Liver Int. 2010;30(7):937–47.
6. Iwakiri Y. Pathophysiology of portal hypertension. Clin Liver Dis. 2014;18(2):281–91.
7. Hou W, Sanyal AJ. Ascites: diagnosis and management. Med Clin North Am. 2009;93(4):801–17.
8. Cirera I, Bauer TM, Navasa M, et al. Bacterial translocation of enteric organisms in patients with cirrhosis. J Hepatol. 2001;34(1):32–7.
9. Singhal S, Baikati KK, Jabbour II, et al. Management of refractory ascites. Am J Ther. 2012;19(2):121–32.
10. Runyon BA, Practice Guidelines Committee, American Association for the Study of Liver Diseases (AASLD). Management of adult patients with ascites due to cirrhosis: update 2012. http://www.aasld.org/publications/practice-guidelines-0.
11. Pirlich M, Selberg O, Böker K, et al. The creatinine approach to estimate skeletal muscle mass in patients with cirrhosis. Hepatology. 1996;24(6):1422–7.
12. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology. 1996;23:164–76.
13. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology. 2003;38(1):258–66.
14. Fukui H, Saito H, Ueno Y, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51(7):629–50.
15. Wong F, Watson H, Gerbes A, et al. Satavaptan for the management of ascites in cirrhosis: efficacy and safety across the spectrum of ascites severity. Gut. 2012;61(1):108–16.
16. Sakaida I, Kawazoe S, Kajimura K, et al. Tolvaptan for improvement of hepatic edema: a phase 3, multicenter, randomized, double-blind, placebo-controlled trial. Hepatol Res. 2014;44(1):73–82.

Chapter 51
Treatment of Refractory Ascites

Makoto Segawa and Isao Sakaida

Abstract In Japan, the primary therapeutic options for refractory ascites include pharmacotherapy with diuretics, paracentesis with albumin infusion, peritoneovenous shunt using Denver shunt, cell-free and concentrated ascites reinfusion therapy (CART), transjugular intrahepatic portosystemic shunt (TIPS), and liver transplantation.

Recently, the novel diuretic tolvaptan (vasopressin V_2 receptor antagonist) has been shown to be effective in the treatment of refractory ascites or hyponatremia in patients with liver cirrhosis. However, a positive effect on the prognosis has not been reported. Patients with diuretic-resistant ascites are often treated by paracentesis with albumin infusion or CART. Although TIPS is effective in controlling refractory ascites, it frequently causes hepatic encephalopathy and requires technical skills to perform. Liver transplantation is the only definitive therapy for refractory ascites; however, it cannot always be performed due to the shortage of donors in Japan.

Keywords Tolvaptan · Paracentesis · Peritoneovenous shunt (Denver shunt) Cell-free and concentrated ascites reinfusion therapy (CART) · Transjugular intrahepatic portosystemic shunt (TIPS)

M. Segawa
Department of Kampo Medicine, Yamaguchi University Hospital, Ube, Yamaguchi, Japan

I. Sakaida (✉)
Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan
e-mail: sakaida@yamaguchi-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_51

51.1 Introduction

Although liver transplantation is a final therapeutic option for refractory ascites, the number of patients in Japan who receive a cadaveric liver transplantation is very small compared with that in Europe and the United States. The total number of liver transplants performed in Japan in 2014 was 463, comprising 418 living-donor transplants and 45 cadaveric-donor transplants. This number includes patients with all liver diseases, including liver cirrhosis. The small number of transplants is because of the shortage of donors in Japan. When liver transplantation cannot be performed, treatment other than liver transplantation is often the final treatment in Japan.

In this chapter, we give an overview of individual treatments for refractory ascites performed in Japan.

51.2 Pharmacotherapy Using Diuretics

51.2.1 Efficacy of Tolvaptan for Ascites Showing Refractoriness to Conventional Diuretics

Nonpeptide arginine vasopressin (AVP) receptor antagonists, known as vaptans, were developed in the 1990s as novel diuretic drugs for edema in patients with liver cirrhosis or heart failure or for hyponatremia in patients with the syndrome of inappropriate secretion of antidiuretic hormone. Vaptans, including mozavaptan, lixivaptan, satavaptan, and tolvaptan, induce a highly hypotonic diuresis without affecting the excretion of electrolytes. Tolvaptan (7.5 mg/day) was approved in Japan in 2013 for treatment of body fluid retention in cirrhosis when treatment with conventional diuretic drugs, such as furosemide or spironolactone, is not effective. Since then, tolvaptan has become the primary treatment option for cirrhotic ascites in Japan.

Tolvaptan blocks the effect of AVP and increases the clearance of electrolyte-free water without changing the total level of electrolyte excretion by binding to the V_2 receptor in the renal collecting duct [1]. The clinical trial performed in Japan showed that tolvaptan produced a decrease in body weight, reduction in ascitic fluid volume, and an increase in urine volume compared with placebo, despite the use of conventional diuretics [2–5]. Tolvaptan has been shown to be effective for ascites complicated by decompensated cirrhosis with decreased albumin synthesis. Approximately 60% of the patients with edema-related symptoms, including bloating, loss of appetite, malaise, sensation of pressure when lying down, and breathing difficulty, improved [3]. Low–dose tolvaptan (3.75 mg/day) was also effective. The efficacy of tolvaptan for refractory ascites is reported to be 63.3% [6] and 89.7% [7].

51.2.2 Importance of Renal Protection in Use of Diuretics

Deterioration of renal function is frequently observed with diuretic therapy. Treatment with spironolactone (200–400 mg/day) plus furosemide (40–240 mg/day) is associated with a significant increase in serum creatinine and blood urea nitrogen (BUN) [8]. Acute kidney injury in cirrhotic patients is also related to a significant reduction in survival [9]. Recently, the International Ascites Club (IAC) proposed new diagnostic criteria for hepatorenal syndrome based on diagnostic criteria of acute kidney injury and emphasized the importance of renal protection by early diagnosis of clinical stage and appropriate therapeutic intervention [10].

In our small group study comparing responders (weight loss >2 kg after 1 week of treatment with tolvaptan) and nonresponders (weight loss <2 kg after 1 week of treatment with tolvaptan), serum creatinine before administration of tolvaptan and cumulative survival rate were significantly higher in responders than in nonresponders. This result suggests that tolvaptan should be administrated at an early stage in which renal function is normal [11]. We also demonstrated in our case report that tolvaptan, after becoming ineffective against refractory ascites, becomes effective again after discontinuation of furosemide [12]. It will be necessary to determine the appropriate combination of diuretics and timing of administration.

51.2.3 Therapeutic Roles of Tolvaptan in Patients with Liver Cirrhosis

The therapeutic goals in patients with liver cirrhosis are recovery of liver function, improvement of quality of life (QOL) through control of liver cirrhosis-related complications, and improvement of the prognosis [13] (Fig. 51.1). The choice of

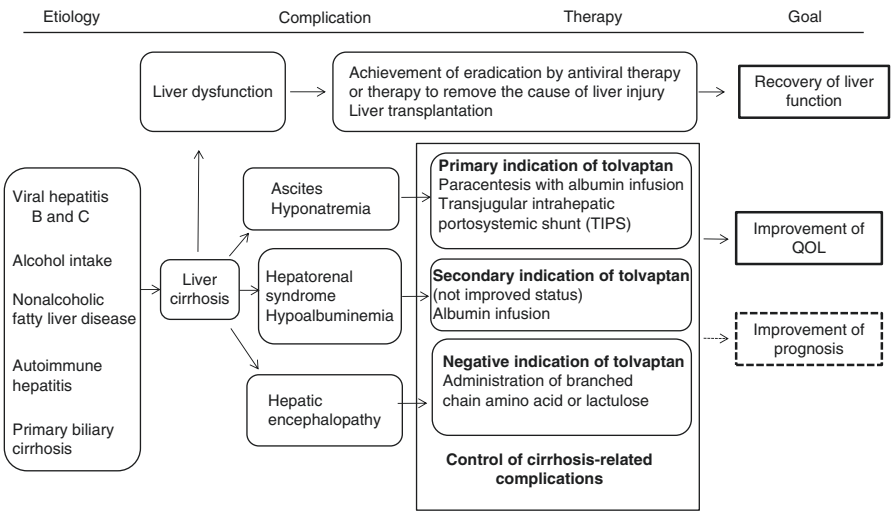


Fig. 51.1 Therapeutic roles of tolvaptan in patients with liver cirrhosis

therapeutic strategy depends on the etiology of cirrhosis, liver function, and complications, such as hyponatremia, ascites, hepatorenal syndrome, hypoalbuminemia, and hepatic encephalopathy. Therapy to remove the cause of liver injury and liver transplantation are the primary therapies to restore liver function and should be considered first. The goals of tolvaptan therapy are improvement in QOL and prognosis by amelioration of liver cirrhosis-related symptoms.

With regard to improvement of QOL, in clinical trials in Japan, tolvaptan not only caused a significant decrease in body weight and an increase in serum sodium concentration but also improved bothersome cirrhosis-related symptoms [3]. A subanalysis of the Study of Ascending Levels of Tolvaptan trials reported a significant improvement in the mental component summary scores of the Short Form-12 Health Survey in hyponatremic patients receiving tolvaptan [14]. These results indicate that tolvaptan improves QOL by removing bothersome cirrhosis-related symptoms.

Recently, the Food and Drug Administration (FDA) recommended that tolvaptan should not be used for >30 days and should not be used in patients with underlying liver disease due to the possibility of liver injury. However, worsening of liver function caused by tolvaptan seems to be rare and idiosyncratic and also reversible. A recent meta-analysis showed that vaptans have a small beneficial effect on hyponatremia and ascites but do not affect mortality, complications of cirrhosis, or renal failure [15].

In Japan, 7.5 mg/day of tolvaptan is used as a safe and effective therapeutic drug for ascites that is resistant to conventional diuretics, and it is approved by the national health-care insurance system. In a Japanese clinical trial [3], tolvaptan was administered to patients who had refractory ascites in an early clinical stage, in which renal function was not impaired by a large volume of conventional diuretics. Appropriate timing of the administration of tolvaptan and combining tolvaptan with small doses of conventional diuretics in early clinical stages, preserving normal renal function, might help improve the efficacy of tolvaptan.

51.3 Paracentesis with Albumin Infusion

Paracentesis with albumin infusion is performed as a treatment for refractory ascites that is resistant to diuretics. This treatment quickly relieves abdominal symptoms, such as sensation of abdominal fullness and dyspnea. However, it needs to be frequently repeated because of recurrence of ascites. Although rapid, large-volume paracentesis may induce hepatic coma and renal failure, infusion of albumin after paracentesis can prevent worsening of the general circulation. To administer this treatment safely, it is desirable to keep the drainage speed at <1000–2000 mL/h and the drainage volume for each session at <1000–3000 mL.

Current European and American guidelines recommend albumin infusion when performing large-volume paracentesis (LVP; i.e., >5 L removed), because albumin infusion prevents 85% of cirrhotic patients from developing paracentesis-induced circulatory dysfunction (PICD) [16, 17]. LVP with albumin infusion is also recommended in Japanese clinical practice guidelines for liver cirrhosis; however, infusion is restricted to 20–25% albumin at 50 mL/day up to six times per month by the national health-care insurance system [18].

A recent meta-analysis demonstrated that PICD is associated with high rates of recurrence of ascites, development of hepatorenal syndrome, dilutional hyponatremia, and mortality [19]. Albumin decreased morbidity and mortality among patients with tense ascites undergoing LVP, as compared with alternative treatments, such as artificial colloids and vasoconstrictors [19]. On the basis of this result, albumin has been proposed as the best plasma volume expander to prevent PICD and hyponatremia after paracentesis [18]. LVP is a safe and effective therapeutic option for temporary palliation of refractory ascites, but it does not improve the prognosis.

51.4 Ascites Reinjection Method

51.4.1 Peritoneovenous Shunt (Denver Shunt)

The PV shunt is designed to transport ascitic fluid into the venous circulation continuously in cirrhotic patients with intractable ascites. The LeVeen shunt was the first design used clinically [20]; only the Denver shunt is now available. The Denver shunt has a subcutaneous compressible valve chamber that can be flushed manually and has a better patency rate [21]. The PV shunt is effective in relieving refractory ascites and improving QOL, although it does not affect the natural course of cirrhosis or its complications.

The PV shunt is rarely used now [16, 17] because of poor long-term patency, frequent complications, and no survival advantage compared with other medical therapies in controlled trials [22, 23]. A randomized, controlled trial of uncoated transjugular intrahepatic portosystemic shunt (TIPS) versus PV shunt showed better long-term efficacy in the TIPS group [24]. Reported complications of the PV shunt are shunt occlusion, infection, disseminated intravascular coagulation, deep vein thrombosis, and catheter breaks and leaks. Because of its high rate of complications, the PV shunt has been virtually abandoned and is reserved for diuretic-resistant ascites patients who are not candidates for transplantation or TIPS and who are not candidates for serial paracentesis because of obesity or too many abdominal surgical scars to receive safe and successful paracentesis.

The PV shunt is not commonly used in Japan as a conservative therapy for refractory ascites, either. The Japanese clinical practice guidelines for liver cirrhosis state that the PV shunt may be used in patients when other treatments are not applicable [18].

51.4.2 Cell–Free and Concentrated Ascites Reinfusion Therapy (CART)

CART is a therapeutic procedure that reuses drained ascitic fluid, which is filtered to remove bacteria and cell fractions, concentrated, and reinfused intravenously. This method was introduced clinically in the 1970s, and the design of the apparatus has been improved. The CART system was approved by the national health-care insurance system in 1981, and it is used as a treatment for refractory ascites. This procedure has the benefit of decreasing albumin use and has no risk of infection by an unknown pathogen from plasma albumin derived from blood donation.

The reported clinical benefits are palliation of sensation of abdominal fullness, reduction of abdominal pressure, increase of circulating plasma volume and plasma osmotic pressure, re-expression of the diuretic effect, and extension of the ascites retention interval. CART is reported to be as safe and effective as LVP with albumin infusion, and no significant difference between CART and LVP was found in survival rate or recurrence of tense ascites during 2 years of observation [25]. CART does not affect liver function, coagulation parameters, or platelet count [26].

The high cost and complications of performing the procedure are disadvantages. A transient decrease in platelet count and fibrinogen or development of a fever is sometimes observed. CART is not recommended in patients with complications of spontaneous bacterial peritonitis or a high level of endotoxin in the ascitic fluid, because endotoxin in the ascitic fluid is concentrated by this procedure. The recommended speed of filtration and concentration is 1000–2000 mL/h, and the recommended speed of reinfusion is 100–150 mL/h because pyrexia frequently occurs if the ascitic fluid is processed too fast [27].

51.5 Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS is a therapeutic procedure for complications of portal hypertension, including refractory ascites. The mechanism for improving ascites involves increased natriuresis via reductions in proximal tubular sodium reabsorption and in the renin-angiotensin-aldosterone system [28]. Compared with LVP with albumin infusion, TIPS is more effective in controlling ascites, preventing its recurrence, and improving mental QOL and survival [29–31]. TIPS frequently causes hepatic encephalopathy and requires technical skills to perform; however, it can be recommended for appropriate selected patients [18].

References

1. Doggrell SA. Tolvaptan (Otsuka). Curr Opin Investig Drugs. 2004;5(9):977–83.
2. Okita K, Kawazoe S, Hasebe C, et al. Dose-finding trial of tolvaptan in liver cirrhosis patients with hepatic edema: a randomized, double-blind, placebo-controlled trial. Hepatol Res. 2014;44(1):83–91.

3. Sakaida I, Kawazoe S, Kajimura K, et al. Tolvaptan for improvement of hepatic edema: a phase 3, multicenter, randomized, double-blind, placebo-controlled trial. Hepatol Res. 2014;44(1):73–82.
4. Sakaida I, Nakajima K, Okita K, et al. Can serum albumin level affect the pharmacological action of tolvaptan in patients with liver cirrhosis? A post hoc analysis of previous clinical trials in Japan. J Gastroenterol. 2015;50(10):1047–53.
5. Sakaida I, Okita K. Correlation between changes in bodyweight and changes in ascites volume in liver cirrhosis patients with hepatic edema in short-term diuretic therapy. Hepatol Res. 2014;44(7):735–9.
6. Ohki T, Sato K, Yamada T, et al. Efficacy of tolvaptan in patients with refractory ascites in a clinical setting. World J Hepatol. 2015;7(12):1685–93.
7. Zhang X, Wang SZ, Zheng JF, et al. Clinical efficacy of tolvaptan for treatment of refractory ascites in liver cirrhosis patients. World J Gastroenterol. 2014;20(32):11400–5.
8. Ginés P, Arroyo V, Quintero E. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. Gastroenterology. 1987;93(2):234–41.
9. Tsien CD, Rabie R, Wong F. Acute kidney injury in decompensated cirrhosis. Gut. 2013;62(1):131–7.
10. Angeli P, Ginès P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol. 2015;62(4):968–74.
11. Iwamoto T, Maeda M, Hisanaga T, et al. Predictors of the effect of tolvaptan on prognosis of cirrhosis. Intern Med. 2016;55(20):2911–6.
12. Goto A, Terai S, Nakamura M, et al. Re-response to tolvaptan after furosemide dose reduction in a patient with refractory ascites. Clin J Gastroenterol. 2015;8(1):47–51.
13. Sakaida I. Tolvaptan for the treatment of liver cirrhosis oedema. Expert Rev Gastroenterol Hepatol. 2014;8(5):461–70.
14. Cárdenas A, Ginès P, Marotta P, et al. Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis. J Hepatol. 2012;56(3):571–8.
15. Dahl E, Gluud LL, Kimer N, et al. Meta-analysis: the safety and efficacy of vaptans (tolvaptan, satavaptan and lixivaptan) in cirrhosis with ascites or hyponatraemia. Aliment Pharmacol Ther. 2012;36(7):619–26.
16. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53(3):397–417.
17. Runyon BA. AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013;57(4):1651–3.
18. Fukui H, Saito H, Ueno Y, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51(7):629–50.
19. Bernardi M, Caraceni P, Navickis RJ, et al. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology. 2012;55(4):1172–81.
20. Leveen HH, Christoudias G, Ip M, et al. Peritoneo-venous shunting for ascites. Ann Surg. 1974;180(4):580–91.
21. Martin LG. Percutaneous placement and management of the Denver shunt for portal hypertensive ascites. AJR Am J Roentgenol. 2012;199(4):W449–53.
22. Stanley MM, Ochi S, Lee KK, et al. Peritoneovenous shunting as compared with medical treatment in patients with alcoholic cirrhosis and massive ascites. Veterans Administration Cooperative Study on Treatment of Alcoholic Cirrhosis with Ascites. N Engl J Med. 1989;321(24):1632–8.
23. Ginès P, Arroyo V, Vargas V, et al. Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. N Engl J Med. 1991;325(12):829–35.
24. Rosemurgy AS, Zervos EE, Clark WC, et al. TIPS versus peritoneovenous shunt in the treatment of medically intractable ascites: a prospective randomized trial. Ann Surg. 2004;239(6):883–9; discussion 889–91.

25. Graziotto A, Rossaro L, Inturri P, et al. Reinfusion of concentrated ascitic fluid versus total paracentesis. A randomized prospective trial. Dig Dis Sci. 1997;42(8):1708–14.
26. Bernardi M, Rimondi A, Gasbarrini A, et al. Ascites apheresis, concentration and reinfusion for the treatment of massive or refractory ascites in cirrhosis. J Hepatol. 1994;20(2):289–95.
27. Takamatsu S, Miyazaki H, Katayama K, et al. Current status of CART for refractory ascites. Kan Tan Sui. 2003;46(5):663–9. (in Japanese)
28. Patidar KR, Sydnor M, Sanyal AJ. Transjugular intrahepatic portosystemic shunt. Clin Liver Dis. 2014;18(4):853–76.
29. Salerno F, Camma C, Enea M, et al. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. Gastroenterology. 2007;133:825–34.
30. Bai M, Qi XS, Yang ZP, et al. TIPS improves liver transplantation-free survival in cirrhotic patients with refractory ascites: an updated meta-analysis. World J Gastroenterol. 2014;20:2704–14.
31. Campbell MS, Brensinger CM, Sanyal AJ, et al. Quality of life in refractory ascites: transjugular intrahepatic portal-systemic shunting versus medical therapy. Hepatology. 2005;42:635–40.

Part VII
Complications of Portal Hypertension: Spontaneous Bacterial Peritonitis

Chapter 52
Diagnosis of Spontaneous Bacterial Peritonitis

Hiroko Setoyama, Motohiko Tanaka, and Yutaka Sasaki

Abstract Spontaneous bacterial peritonitis (SBP) is an infection of ascites that occurs in the absence of an apparent source of infection. Bacterial translocation from the gut plays an important role in developing SBP. Bacteria that eventually cause SBP can also originate from sites other than the gut via bacteremic seeding. The vast majority of patients with SBP have advanced cirrhosis. Although SBP patients develop symptoms such as fever and abdominal pain, some have no signs or symptoms of infection at the time of diagnosis. Early diagnosis is a key issue in the management of SBP. Patients with ascites admitted to the hospital should undergo abdominal paracentesis. The ascitic fluid should be tested for aerobic and anaerobic cultures, white blood cell count and differential, and fluid chemistries. A confirmed SBP diagnosis requires a positive ascitic fluid bacterial culture, with an elevated ascitic fluid absolute polymorphonuclear leukocyte count and without any evidence of an intra-abdominal surgically treatable source. Pathogens commonly associated with SBP include *Escherichia coli*, streptococcal species, and *Klebsiella pneumoniae*. As appropriate therapy is necessary for a good prognosis, a clear distinction is crucial (or mandatory) between secondary bacterial peritonitis and SBP.

Keywords Paracentesis · Polymorphonuclear leukocyte (PMN) count · Bacterial translocation

52.1 Introduction

As ascitic fluid infection is commonly observed in patients with cirrhosis and ascites, paracentesis is considered to be a crucial diagnostic procedure [1]. Spontaneous bacterial peritonitis (SBP) is defined as an ascitic fluid infection without an evident intra-abdominal surgically treatable source [2]. When first described, its mortality exceeded 90%. With early recognition of the disease and prompt and appropriate

H. Setoyama · M. Tanaka · Y. Sasaki (✉)
Department of Gastroenterology and Hepatology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Kumamoto, Japan
e-mail: sasakiy@kumamoto-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_52

antibiotic therapy, in-hospital mortality for an episode of SBP has been reduced to around 20%. In patients who survive an episode of SBP, the 1-year cumulative recurrence is high, with rates at approximately 70% [3, 4]. However, patients with severely disturbed liver function still have a poor long-term prognosis [5–7].

52.2 Pathogenesis

The pathogenesis of spontaneous ascitic fluid infection involves the translocation of bacteria from the gut to the mesenteric lymph nodes, disturbed reticuloendothelial phagocytic activity, and deficient ascitic fluid antibacterial activity [8]. Bacteria that eventually cause SBP can also originate from sites other than the gut via bacteremic seeding (i.e., urinary tract infections [9], pneumococcal sepsis [8], and dental infections).

Furthermore, cirrhosis is actually one of the most common forms of acquired immune deficiency, which creates an environment that facilitates the persistence of the peritoneal infection [10]. The relevance of the ascitic fluid protein concentration as a predictor of SBP development in cirrhotic patients can be explained by the direct relationship between this parameter and the ascitic fluid opsonic activity along with the concentration of defensive substances in the ascites, such as complement, immunoglobulins, and fibronectin [11].

52.3 Predisposing Factors

Severity of the liver disease is probably the most important factor. Almost 70% of the patients who develop SBP are classified as Child-Pugh class C, with the remainder classified as class B. A serum total bilirubin level of >2.5 mg/dL is an independent predictive factor of SBP [6]. Other risk factors are as follows [6, 12]:

- Ascitic fluid total protein level <1 g/dL.
- Previous SBP episodes.
- Gastrointestinal bleeding.
- Urinary tract infection.
- Intestinal bacterial overgrowth.
- Iatrogenic factors: Urinary bladder and intravascular catheter.

52.4 Clinical Manifestations

The most common symptoms are fever (69%) and abdominal pain (59%). Other signs and symptoms include hepatic encephalopathy (54%), abdominal tenderness (49%), diarrhea (32%), ileus (30%), shock (21%), and hypothermia (17%) [2]. In

contrast, approximately 13% of the patients with SBP have no signs or symptoms of the infection at the time of diagnosis [13]. A rigid abdomen does not occur in patients with infected ascites, since ascites separate the visceral from the parietal peritoneal surfaces [14]. Thus, in order for a clinician to diagnose SBP at a relatively early stage of the infection, there needs to be a high index of suspicion. The effective treatment period for ensuring a good outcome is frequently very short [15].

52.5 Diagnosis

52.5.1 Paracentesis

The American Association for the Study of Liver Diseases (AASLD) practice guidelines on the management of adult patients with ascites due to cirrhosis recommend that when ascites patients are admitted to the hospital, they should undergo abdominal paracentesis [16]. This guideline also recommends that paracentesis be repeated in patients (whether in the hospital or not) who develop signs or symptoms or laboratory abnormalities suggestive of infection (e.g., abdominal pain, tenderness, fever, encephalopathy, renal failure, acidosis, or peripheral leukocytosis) [16]. The findings from a review of a database of 17,711 patients with cirrhosis and ascites who were admitted to a hospital with a primary diagnosis of ascites or encephalopathy demonstrated the importance of paracentesis. In 61% of the patients who underwent paracentesis, these subjects had a lower in-hospital mortality rate than those who did not [17]. Before a confident diagnosis of ascitic fluid infection can be made, abdominal paracentesis must be performed, with the ascitic fluid, and then analyzed [14]. Moreover, it is also recommended that a diagnostic paracentesis also be performed in patients with gastrointestinal bleeding, shock, fever, or other signs of systemic inflammation and gastrointestinal symptoms, as well as in patients with worsening liver and/or renal function and hepatic encephalopathy in accordance with the European Association for the Study of the Liver (EASL) clinical practice guidelines [18].

52.5.2 Ascitic Fluid Analysis

The diagnosis of SBP is made when there are a positive ascitic fluid bacterial culture and an elevated absolute polymorphonuclear leukocyte (PMN) count (i.e., $\geq$250 cells/mm^3) in the ascitic fluid without an evident intra-abdominal, surgically treatable source of infection [19]. The ascitic fluid also needs to be tested for aerobic and anaerobic cultures, cell count and differential, and fluid chemistries (albumin, protein, glucose, lactate dehydrogenase, amylase, and in some cases bilirubin).

52.5.3 Ascitic Fluid Culture

A positive ascitic fluid culture not only confirms a diagnosis of SBP but also allows for tailored antibiotic therapy. However, there should be no delay in starting the antibiotic therapy while awaiting culture results in SBP patients. Patients should be treated with broad-spectrum antibiotics, with a narrowing of the antibiotic coverage once the pathogen has been identified. Pathogens commonly associated with SBP include *Escherichia coli*, streptococcal species, and *Klebsiella pneumoniae* [20].

Patients with a PMN count ≥250 cells/mm^3 in the ascitic fluid and with a negative culture are considered to have culture-negative SBP [21]. Clinical presentation of culture-negative SBP is similar to that for the culture-positive SBP, and thus, culture-negative SBP should be treated in a similar manner [22]. In some patients, however, the ascitic PMN count is less than 250/mm^3, even though they have a positive ascitic fluid culture. This condition is known as bacterascites. If patients with bacterascites exhibit signs of systemic inflammation or infection, then they need to be treated with antibiotics. Meanwhile, patients who are asymptomatic need to undergo a second paracentesis after 48 h. Patients having a repeated ascitic PMN count of ≥250/mm^3 should be treated for SBP, while patients with a PMN count <250/mm^3 need to be followed up [18, 23].

52.5.4 Secondary Bacterial Peritonitis

Secondary bacterial peritonitis is defined as a condition where the peritonitis is due to perforation or inflammation of an intra-abdominal organ. This condition should be suspected in patients who have localized abdominal symptoms or signs, presence of multiple organisms upon ascitic culture, a very high ascitic PMN count, and/or high ascitic protein concentration or in patients who exhibit an inadequate response to the initial therapy [24]. Due to the importance of being able to administer the appropriate therapy in patients, the ability to distinguish between secondary bacterial peritonitis and SBP is crucial. Unfortunately, signs and symptoms cannot help in separating patients who need surgical intervention from those who need antibiotic treatment for SBP. However, the initial ascitic fluid analysis and responses to treatment can assist in helping to make this important distinction [14]. The AASLD practice guidelines recommend that when the ascitic fluid of a patient with cirrhosis exhibits a PMN count ≧250 cells/mm^3 and there is a high suspicion of secondary peritonitis, these patients should also be tested for total protein, LDH, glucose, Gram stain, carcinoembryonic antigen (CEA), and alkaline phosphatase (ALP) in order to distinguish SBP from secondary peritonitis (Fig. 52.1) [16]. Furthermore, having patients undergo appropriate radiological examinations such as CT scanning can also be very useful [24].

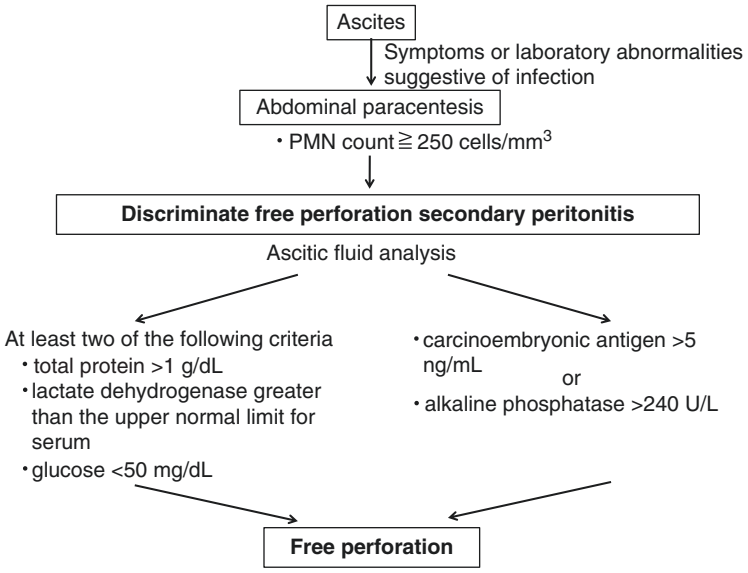


Fig. 52.1 Discriminating free perforation secondary peritonitis

References

1. Borzio M, Salerno F, Piantoni L, Cazzaniga M, Angeli P, Bissoli F, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. Dig Liver Dis. 2001;33:41–8.
2. Such J, Runyon BA. Spontaneous bacterial peritonitis. Clin Infect Dis. 1998;27:669–74; quiz 666–675.
3. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis. 2008;28:26–42.
4. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Gastroenterology. 2001;120:726–48.
5. Navasa M, Follo A, Llovet JM, Clemente G, Vargas V, Rimola A, et al. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. Gastroenterology. 1996;111:1011–7.
6. Andreu M, Sola R, Sitges-Serra A, Alia C, Gallen M, Vila MC, et al. Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. Gastroenterology. 1993;104:1133–8.
7. Tito L, Rimola A, Gines P, Llach J, Arroyo V, Rodes J. Recurrence of spontaneous bacterial peritonitis in cirrhosis: frequency and predictive factors. Hepatology. 1988;8:27–31.
8. Guarner C, Runyon BA. Spontaneous bacterial peritonitis: pathogenesis, diagnosis, and management. Gastroenterologist. 1995;3:311–28.
9. Ho H, Zuckerman MJ, Ho TK, Guerra LG, Verghese A, Casner PR. Prevalence of associated infections in community-acquired spontaneous bacterial peritonitis. Am J Gastroenterol. 1996;91:735–42.
10. Runyon BA. Bacterial infections in patients with cirrhosis. J Hepatol. 1993;18:271–2.
11. Reider H, Ramadori G, Meyer zum Buschenfelde KH. Opsonic activity of human ascitic fluid. Hepatology. 1986;6:545–6.

12. Runyon BA. Patients with deficient ascitic fluid opsonic activity are predisposed to spontaneous bacterial peritonitis. Hepatology. 1988;8:632–5.
13. Runyon BA. Monomicrobial nonneutrocytic bacterascites: a variant of spontaneous bacterial peritonitis. Hepatology. 1990;12:710–5.
14. Akriviadis EA, Runyon BA. Utility of an algorithm in differentiating spontaneous from secondary bacterial peritonitis. Gastroenterology. 1990;98:127–33.
15. Hoefs JC, Runyon BA. Spontaneous bacterial peritonitis. Dis Mon. 1985;31:1–48.
16. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009;49:2087–107.
17. Orman ES, Hayashi PH, Bataller R, Barritt AS. Paracentesis is associated with reduced mortality in patients hospitalized with cirrhosis and ascites. Clin Gastroenterol Hepatol. 2014;12:496–503 e491.
18. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53:397–417.
19. Hoefs JC, Canawati HN, Sapico FL, Hopkins RR, Weiner J, Montgomerie JZ. Spontaneous bacterial peritonitis. Hepatology. 1982;2:399–407.
20. Fernandez J, Navasa M, Gomez J, Colmenero J, Vila J, Arroyo V, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology. 2002;35:140–8.
21. Runyon BA, Hoefs JC. Culture-negative neutrocytic ascites: a variant of spontaneous bacterial peritonitis. Hepatology. 1984;4:1209–11.
22. Terg R, Levi D, Lopez P, Rafaelli C, Rojter S, Abecasis R, et al. Analysis of clinical course and prognosis of culture-positive spontaneous bacterial peritonitis and neutrocytic ascites. Evidence of the same disease. Dig Dis Sci. 1992;37:1499–504.
23. Rimola A, Garcia-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol. 2000;32:142–53.
24. Guarner C, Soriano G. Spontaneous bacterial peritonitis. Semin Liver Dis. 1997;17:203–17.

Chapter 53
Treatment of Spontaneous Bacterial Peritonitis

Hiroko Setoyama, Motohiko Tanaka, and Yutaka Sasaki

Abstract After the diagnosis of spontaneous bacterial peritonitis (SBP), patients should immediately receive empiric antibiotic treatment. Until the results of susceptibility testing are available, broad-spectrum therapy is warranted in patients with a suspected ascitic fluid infection. A reasonable choice for suspected SBP is a third-generation cephalosporin, preferably cefotaxime 2 g every 8 h. In uncomplicated SBP, oral ofloxacin (400 mg twice per day for an average of 8 days) also provides similar results as intravenous cefotaxime. Intravenous albumin infusions can also decrease the risk of renal impairment that often develops in patients with SBP. Several randomized controlled trials have reported that the administration of antibiotic prophylaxis in high-risk SBP patients can decrease the risk of bacterial infection and mortality. However, in order to minimize bacterial resistance, it is necessary to restrict the use of these prophylactic antibiotics to patients who demonstrate the well-defined criteria for SBP prophylaxis.

Keywords Empirical antibiotic therapy · Cefotaxime · Intravenous albumin infusion · Prophylactic regimen · Norfloxacin · Bacterial resistance

53.1 Introduction

Spontaneous bacterial peritonitis (SBP) is an infection of ascites that occurs in the absence of a contiguous source of infection. Diagnosis of SBP is based on the polymorphonuclear leukocyte (PMN) count in ascitic fluid. The cutoff PMN count that has been reported to show the best sensitivity for the diagnosis of SBP is 250 cells/mm^3 [1]. In order to ensure that these diagnoses are made at a relatively earlier stage of infection, clinicians need to be aware of these potential infections and carefully examine these types of patients. Clinicians should also be aware of a very short

H. Setoyama · M. Tanaka · Y. Sasaki (✉)
Department of Gastroenterology and Hepatology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Kumamoto, Japan
e-mail: sasakiy@kumamoto-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_53

window of opportunity during which interventions can be made in order to ensure a good outcome [2]. In this chapter, we review the treatment and prophylaxis for SBP.

53.2 Treatment of SBP

53.2.1 Empirical Antibiotic Therapy (Table 53.1)

Once the diagnosis of SBP has been established by the finding that the ascitic fluid PMN counts are ≧250 cells/mm^3, patients should immediately receive empiric antibiotic therapy [3]. Since the ascitic fluid PMN count can be obtained more rapidly than results from a culture, this can be used to reliably identify patients who need empiric antibiotic coverage [4]. If the start of the treatments is delayed after finding that an ascitic fluid culture can grow bacteria, this could lead to a patient's death from an overwhelming infection. Therefore, broad-spectrum antibiotics are recommended in patients with suspected ascitic fluid infection until the results of susceptibility testing become available. A third-generation cephalosporin is a reasonable choice for suspected SBP, as it covers 95% of the flora including the three most common isolates: *Escherichia coli*, *Klebsiella pneumonia*, and pneumococci [5]. Cefotaxime has been shown to be superior to ampicillin plus tobramycin in a controlled trial [6]. As administration of cefotaxime 2 g intravenously every 8 hours has been shown to significantly improve ascitic fluid levels [7], the American Association for the Study of Liver Diseases (AASLD) practice guidelines have recommended its use in these patients [8]. Lower or less frequent dosing is also applicable, especially in patients with impaired renal function. A previous study has demonstrated that cefotaxime at a dose of 2 g every 6 hours was as effective as a 2 g dose every 12 hours [9]. A randomized controlled trial involving 100 patients found that a

Table 53.1 Antibiotic therapy of SBP

References	Treatments	*N*	Infection resolution (%)	*P*
Felisart, 1985 [6]	Cefotaxime vs. ampicillin/tobramycin	73	85 vs. 56	<0.02
Runyon, 1991 [7]	Cefotaxime (2 g/8 h IV)	41	94	
Rimola, 1995 [9]	Cefotaxime (2 g/6 h IV) vs. cefotaxime (2 g/12 h IV)	143	77 vs. 79	NS
Runyon, 1991 [10]	Cefotaxime 5 days vs. 10 days	100	93 vs. 91	NS
Ricart, 2000 [12]	Amoxicillin/clavulanic acid (1/0.2 g/8 h) IV followed by 0.5/0.125 g/8 h PO vs. cefotaxime (1 g/6 h IV)	48	87 vs. 83	NS
Navasa, 1996 [13]	Ofloxacin (400 mg/12 h PO) vs. cefotaxime (2 g/6 h IV)	123	84 vs. 85	NS

5-day treatment exhibited a similar efficacy as a 10-day treatment in SBP patients with complications [10]. Alternative therapeutic options include the administration of amoxicillin/clavulanic acid and quinolones [11]. A further study reported that administration of amoxicillin/clavulanic acid at a dose of 1 g/0.2 g every 8 hours IV followed by 0.5 g/0.125 g every 8 hours PO had similar results with respect to the SBP resolution and mortality as compared with cefotaxime [12]. Oral ofloxacin at a dose of 400 mg twice per day for an average of 8 days also exhibited an efficacy that was similar to that found for intravenous cefotaxime in SBP patients who did not have any complications [13]. However, the administration of quinolones should not be considered in patients taking these antibiotics for prophylaxis of SBP due to the high prevalence of quinolone-resistant bacteria [14]. Therefore, these patients need to be treated with alternative agents.

53.2.2 Intravenous Albumin in Patients with SBP

Renal impairment develops in 30–40% of patients with SBP, which is one of the most important predictors of hospital mortality in cirrhotic patients with SBP [15]. The risk decreases in conjunction with the intravenous albumin levels. A randomized placebo-controlled trial examined patients with SBP without septic shock after being administered cefotaxime alone versus cefotaxime plus 1.5 g albumin per kg body weight within 6 hours of diagnosis followed by 1.0 g/kg body weight on day 3. The combination of intravenous albumin and antibiotic treatment significantly decreased the mortality from 29 to 10% [16]. Thus, albumin infusions need to be administered if the creatinine is >1 mg/dL, the blood urea nitrogen is >30 mg/dL, or the total bilirubin is >4 mg/dL [17]. Furthermore, albumin has been shown to be superior to hydroxyethyl starch in the treatment of SBP [18]. Although the precise mechanism whereby albumin infusion could decrease the mortality of SBP, one of the possible explanations is that albumin, especially redox form, could decrease the oxidative stress in the whole body associated with SBP, in terms of antioxidant function, leading to the improvement of mortality [19].

53.3 Prophylaxis of SBP

Three high-risk SBP patient populations have been identified [11, 20]. These have been defined as follows:

1. Patients with acute gastrointestinal hemorrhage.
   Bacterial infections occur in between 25 and 65% of cirrhotic patients with gastrointestinal bleeding [11, 21, 22].
2. Patients with low-protein-concentration ascites (<10 g/L) and no prior history of SBP (primary prophylaxis).

3. Patients with a previous history of SBP (secondary prophylaxis).
   The cumulative recurrence rate at 1 year is approximately 70% in the patients who survive an episode of SBP [23].

Several randomized controlled trials demonstrated that the administration of antibiotic prophylaxis in these high-risk patients decreased the risk of a bacterial infection and mortality [24–29]; a 400 mg/day oral dose of norfloxacin has been shown to be effective in preventing SBP in cirrhotic patients with a low ascitic fluid protein concentration and in patients with a prior history of SBP [24]. Antibiotic prophylaxis has also been shown to prevent infection in patients with gastrointestinal bleeding [1, 21] and decrease the rate of rebleeding [29].

The prophylactic regimens that have been suggested by the AASLD practice guidelines [8] include:

- Either intravenous ceftriaxone (1 g intravenously daily) for 7 days or a twice-daily 400 mg oral dose of norfloxacin for 7 days should be given to prevent bacterial infection in patients with cirrhosis and gastrointestinal hemorrhage.
- Patients who have survived a previous episode of SBP need to be given long-term prophylaxis consisting of a daily 400 mg dose of norfloxacin (or a once-daily double-strength tablet of trimethoprim/sulfamethoxazole).
- In patients with cirrhosis and ascites but no gastrointestinal bleeding, the long-term use of norfloxacin (or trimethoprim/sulfamethoxazole) can be justified, provided that the ascitic fluid protein is <1.5 g/dL and at least one of the following is present: serum creatinine >1.2 mg/dL, blood urea nitrogen >25 mg/dL, serum sodium <130 mEq/L, or Child-Pugh >9 points with a bilirubin >3 mg/dL.

However, in order to minimize bacterial resistance, the administration of prophylactic antibiotics to patients needs to be restricted to the well-defined criteria for SBP prophylaxis. Furthermore, to limit the duration of antibiotic treatments, the spectrum of coverage needs to be narrowed once the antibiotic susceptibility testing results become available [30, 31].

References

1. Rimola A, Garcia-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. Int Ascites Club J Hepatol. 2000;32:142–53.
2. Hoefs JC, Runyon BA. Spontaneous bacterial peritonitis. Dis Mon. 1985;31:1–48.
3. Hoefs JC, Canawati HN, Sapico FL, Hopkins RR, Weiner J, Montgomerie JZ. Spontaneous bacterial peritonitis. Hepatology. 1982;2:399–407.
4. Such J, Runyon BA. Spontaneous bacterial peritonitis. Clin Infect Dis. 1998;27:669–74. quiz 675-666
5. Chavez-Tapia NC, Soares-Weiser K, Brezis M, Leibovici L. Antibiotics for spontaneous bacterial peritonitis in cirrhotic patients. Cochrane Database Syst Rev. 2009:CD002232.
6. Felisart J, Rimola A, Arroyo V, Perez-Ayuso RM, Quintero E, Gines P, et al. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. Hepatology. 1985;5:457–62.

7. Runyon BA, Akriviadis EA, Sattler FR, Cohen J. Ascitic fluid and serum cefotaxime and desacetyl cefotaxime levels in patients treated for bacterial peritonitis. Dig Dis Sci. 1991;36:1782–6.
8. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009;49:2087–107.
9. Rimola A, Salmeron JM, Clemente G, Rodrigo L, Obrador A, Miranda ML, et al. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective, randomized, multicenter study. Hepatology. 1995;21:674–9.
10. Runyon BA, McHutchison JG, Antillon MR, Akriviadis EA, Montano AA. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. Gastroenterology. 1991;100:1737–42.
11. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53:397–417.
12. Ricart E, Soriano G, Novella MT, Ortiz J, Sabat M, Kolle L, et al. Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. J Hepatol. 2000;32:596–602.
13. Navasa M, Follo A, Llovet JM, Clemente G, Vargas V, Rimola A, et al. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. Gastroenterology. 1996;111:1011–7.
14. Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol. 2014;60:1310–24.
15. Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology. 1994;20:1495–501.
16. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999;341:403–9.
17. Sigal SH, Stanca CM, Fernandez J, Arroyo V, Navasa M. Restricted use of albumin for spontaneous bacterial peritonitis. Gut. 2007;56:597–9.
18. Fernandez J, Monteagudo J, Bargallo X, Jimenez W, Bosch J, Arroyo V, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology. 2005;42:627–34.
19. Setoyama H, Tanaka M, Nagumo K, Naoe H, Watanabe T, Yoshimaru Y, et al. Oral branched-chain amino acid granules improve structure and function of human serum albumin in cirrhotic patients. J Gastroenterol. 2017;52(6):754–65.
20. Runyon BA. Low-protein-concentration ascitic fluid is predisposed to spontaneous bacterial peritonitis. Gastroenterology. 1986;91:1343–6.
21. Bleichner G, Boulanger R, Squara P, Sollet JP, Parent A. Frequency of infections in cirrhotic patients presenting with acute gastrointestinal haemorrhage. Br J Surg. 1986;73:724–6.
22. Bernard B, Cadranel JF, Valla D, Escolano S, Jarlier V, Opolon P. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. Gastroenterology. 1995;108:1828–34.
23. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Gastroenterology. 2001;120:726–48.
24. Soriano G, Guarner C, Teixido M, Such J, Barrios J, Enriquez J, et al. Selective intestinal decontamination prevents spontaneous bacterial peritonitis. Gastroenterology. 1991;100:477–81.
25. Gines P, Rimola A, Planas R, Vargas V, Marco F, Almela M, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. Hepatology. 1990;12:716–24.
26. Soriano G, Guarner C, Tomas A, Villanueva C, Torras X, Gonzalez D, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. Gastroenterology. 1992;103:1267–72.

27. Blaise M, Pateron D, Trinchet JC, Levacher S, Beaugrand M, Pourriat JL. Systemic antibiotic therapy prevents bacterial infection in cirrhotic patients with gastrointestinal hemorrhage. Hepatology. 1994;20:34–8.
28. Fernandez J, Ruiz del Arbol L, Gomez C, Durandez R, Serradilla R, Guarner C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology. 2006;131:1049–56; quiz 1285.
29. Singh N, Gayowski T, Yu VL, Wagener MM. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. Ann Intern Med. 1995;122:595–8.
30. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013;57:1651–3.
31. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Dig Dis. 2016;34:382–6.

Part VIII
Complications of Portal Hypertension: Hepatic Encephalopathy

Chapter 54
Diagnosis of Hepatic Encephalopathy

Kei Moriya, Tadashi Namisaki, Kosuke Kaji, and Hitoshi Yoshiji

Abstract Hepatic encephalopathy (HE) is a neuropsychiatric symptom that co-occurs with various diseases such as acute hepatic failure and liver cirrhosis. Ammonia, which induces brain edema, is the main cause of HE. In the case of zinc or branched-chain amino acid deficiency, hyperammonemia is intensified. Recently, intestinal dysbiosis was revealed to induce intracranial neuroinflammatory responses in a cirrhotic mouse model in which the dysbiosis is similar to that observed in human subjects with cirrhosis. For the precise diagnosis of HE including minimal HE, a combination of quantitative neuropsychological and electrophysiological tests is necessary, but the diagnosis is highly complicated; computer-assisted neuropsychological tests are useful in this regard. While minimal HE could interfere with a patient's quality of life and prognosis, it should be considered as a potential candidate for overt HE and therapeutic intervention. In a prospective study, hyponatremia in a cirrhotic subject was associated with increased mortality and not only affected brain function but also predisposed the patient to HE. The improvement of serum sodium concentration by the administration of vaptans might therefore improve HE.

Keywords Hepatic encephalopathy · Minimal encephalopathy · Portosystemic shunt · Cirrhosis · Hyponatremia

54.1 Introduction

When hepatic encephalopathy (HE) is detected, a deliberate differential diagnosis should be performed, because consciousness disorders have many etiologies (Table 54.1). HE attributed mainly to liver cirrhosis represents a major healthcare burden in cirrhotic patients [1]. A systemic proinflammatory condition could potentiate neuroinflammation and cerebral dysfunction in the setting of

K. Moriya (✉) · T. Namisaki · K. Kaji · H. Yoshiji
Division of Gastroenterology and Hepatology, Third Department of Internal Medicine, Nara Medical University, Kashihara, Nara, Japan
e-mail: moriyak@naramed-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_54

Table 54.1 Differential diagnosis of hepatic encephalopathy

Circulative disorders	Arrhythmia	Sick sinus syndrome, complete AV block, etc.
–	Hypertension	Hypertensive encephalopathy
–	Stroke	Cerebral infarction, subarachnoid hemorrhage
Metabolic disorders	Chemicals	Alcoholic abuse, drug abuse (barbiturates, opioids, etc.), alcohol withdrawal syndrome, Wernicke's encephalopathy
–	Electrolytes	Hypernatremia, hyponatremia, etc.
–	Endocrinology	Adrenal crisis, thyroid crisis, hypothyroidism
–	Insulin	Hyperglycemia, hypoglycemia, diabetic acidosis, etc.
–	Uremia	Uremic acidosis
Respiratory disorders	Hypoxia	Aspiration pneumonia, interstitial pneumonia, COPD, pulmonary infarction, etc.
Neurotic disorders	Syncope	Encephalitis, meningitis, tumor, intracranial hemorrhage, epilepsy, etc.
Mental disorders	Psychiatry	Mental retardants, psychiatric diseases, etc.

hyperammonemia [2]. Indeed, inducing hyperammonemia in cirrhotic patients increases systemic inflammation and promotes neuropsychological disorders [3]. Pathophysiological evidence indicates hyperammonemia and inflammation as the causes of HE [4, 5].

54.2 Pathology

Brain edema caused by intracranial osmotic abnormalities deteriorates the health-related quality of life (HRQOL), because the level of the brain osmolyte myoinositol on magnetic resonance spectroscopy (MRS) has been closely associated with HRQOL in cirrhotic patients [6]. Under normal conditions, ammonia is metabolized through the glutamic acid synthetic cascade, but in the continuous hyperammonemia environment, decreased glutamic acid and increased glutamine lead to abnormal energy metabolism, and brain edema occurs.

HE is a neuropsychiatric symptom that co-occurs with various diseases such as acute hepatic failure and liver cirrhosis. Gamma-aminobutyric acid receptor activation and pseudo-neurotransmitters in the central nervous system may cause HE; however, ammonia, a final metabolite of nitrogen metabolism, is the main cause of HE.

Zinc, which plays an important role in ammonia metabolism, is bound with plasma albumin and amino acids; in cirrhotic patients, however, because of the decreased level of albumin, zinc binds preferably to amino acids than to albumin and is finally excreted into the urine. In addition, diuretics that are often prescribed for edema and ascites inhibit zinc reabsorption at the renal tubules and increase urinary zinc excretion. Moreover, in cirrhotic patients, zinc intake is insufficient due to loss of appetite. Amino acids consisting of nitrogen compounds are predominantly diverted to the urea and detoxified in the liver through the uremic cycle rather than

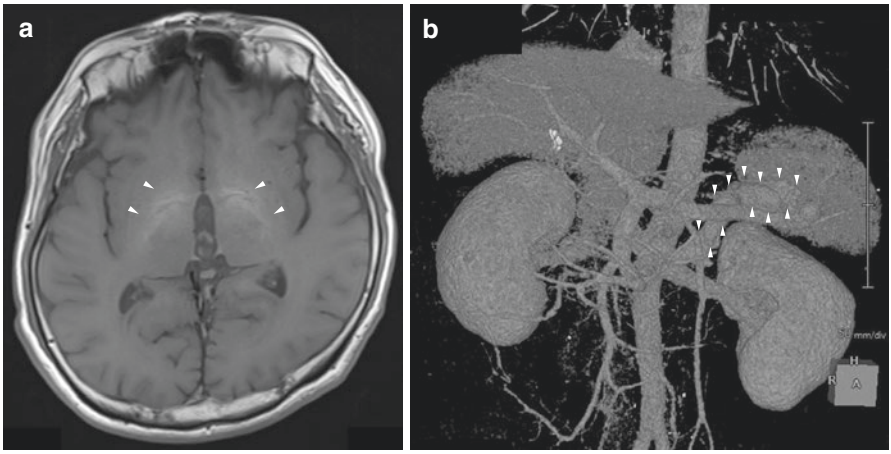


Fig. 54.1 Brain MRI of a patient with persistent hepatic encephalopathy caused by portosystemic shunt. Bilateral hyperintense globus pallidus on T1-weighted MRI in cirrhotic patients (**a**) is associated with the severity of liver failure due to the portosystemic shunt (**b**)

with the glutamine synthetic enzyme. The activity of ornithine transcarbamylase (OTC) is clearly decreased in the case of zinc deficiency, because zinc is essential to its activity.

When ammonia is metabolized through the glutamic acid synthetic cascade in both the brain and skeletal muscle, branched-chain amino acids (BCAA) are indispensable. About one half of the ammonia in the arterial blood flow is metabolized in the skeletal muscle of healthy subjects. However, cirrhotic patients with dysfunction of the uremic cycle attributed to zinc deficiency are obliged to increase the burden of ammonia metabolism on the skeletal muscle, and these mechanisms cause a deficiency of BCAA.

Manganese is a neurotoxin that accumulates in the basal ganglia of patients with portosystemic shunts or cirrhosis [7, 8]. Levels of manganese are associated with the hyperintensity of the nucleus pallidus seen on intracranial magnetic resonance imaging (MRI) (Fig. 54.1).

Cirrhotic patients have imbalanced intestinal flora which are similar to those observed in cirrhotic mice [9, 10], and gut microbiota change could drive the development of neuroinflammatory and systemic inflammatory responses in cirrhotic models [11].

54.3 Clinical Characteristics

HE is classified into acute, chronic, and peculiar types, according to its clinical course and its occurrence. Chronic HE is classified into two different categories: portosystemic shunt dominant and damaged hepatocyte dominant. In the peculiar

type, congenital urea cycle disorders are the most frequent causes, and citrullinemia is the most widespread in adult patients. However, the differential diagnosis between HE with acute liver failure and rapid onset HE in liver cirrhosis is extremely difficult. A case of shunt-induced encephalopathy without liver cirrhosis has been recently reported [12, 13]. Under these circumstances, a new classification has been proposed (Table 54.2) [14, 15].

Subclinical HE (SHE), which gives abnormal results to sensitive quantitative neuropsychiatric function tests without showing any abnormal physical findings, is seen in at least 30% of liver cirrhosis patients [16, 17]. SHE includes preclinical HE and is associated with no clinical symptoms or signs of the degree of coma being grade 1 or 0 according to the conventional grading system [18]. In such a situation, the concept of minimal HE would represent a portion of this dimension on firm statistical grounds [14]. The West Haven criteria (Table 54.3) [14, 19] are widely applied to assess mental state but are not sufficiently detailed, at present, to allow for easy distinction between grade 1 and grade 0. A simple refinement that includes quantitative neuropsychological tests might facilitate this differentiation in the clinical setting (Table 54.4) [20].

Table 54.2 Clinical classification of hepatic encephalopathy

Classifications	Hepatic failure	Extrahepatic portosystemic shunting	Special features
Type A **A**cute liver failure	Severe	Absent	Developed brain edema and intracranial hypertension
Type B Portal-systemic **b**ypass	Mild to moderate (without cirrhosis)	Generally large	Known as Dr. Inose's hepatic encephalopathy (sometime coexisted with idiopathic portal hypertension)
Type C **C**irrhosis	Depends on hepatic functional reserve	Depends on each case	Low-grade cerebral edema without overt signs of intracranial hypertension
1. Minimal encephalopathy	Variable (often mild to moderate)	Not developed	Requires neuropsychological and/or neurophysiological testing for diagnosis (NCT[a], electroencephalography, evoked potentials, P300[b], etc.)
2. Episodic encephalopathy	Variable (often moderate to severe)	Variable	Precipitant induced (infection, bleeding in digestive organs, constipation, over-intake of protein, dehydration, drugs, etc.)
3. Persistent encephalopathy	Variable (often moderate to severe)	Generally large	Known as Dr. Inose's hepatic encephalopathy and also seen after portocaval surgery or TIPS[c]

[a]*NCT* number connection test
[b]*P300* type of auditory evoked potential
[c]TIPS transjugular intrahepatic portosystemic shunt (Based on Ferenci P et al. [14], Stojanov DB et al. [15])

Table 54.3 The West Haven criteria

Grade 0	Lack of detectable changes in personality or behavior No asterixis
Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition Asterixis may be present
Grade 2	Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behavior, slurred speech Impaired performance of subtraction Asterixis is present
Grade 3	Somnolence to semi-stupor, but responsive to verbal stimuli Confusion Gross disorientation Asterixis is usually absent
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Hepatic encephalopathy is classified into these five grades according to the West Haven criteria (Based on Ferenci P et al. [14], Atterbury CE et al. [19]).

Table 54.4 Newly proposed modification of the West Haven criteria for the grading of mental state in cirrhotic patients

Grade	Description	Proposed operative definition
0	No abnormality detected	–
1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction	Not able to complete TMT-A[a] in 120 s (individuals with ≥5 years of education) or naming ≤7 animals in 120 s Orientated in time and space
2	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior	Disorientated in time: (>3 items incorrect) Day of the week/day of the month The month/the year Orientated in place
3	Somnolence to semi-stupor Responsive to stimuli Confused Gross disorientation Bizarre behavior	Disorientated in place: (≥2 items incorrect) State/country Region/country City/place/floor/ward Disorientated in time Reduction of Glasgow score (8–14)
4	Coma, unable to test mental state	Unresponsive to pain stimuli (Glasgow score < 8)

[a]*TMT-A* trail making test A (Adapted from Amodio P et al. [20]).

Electroencephalogram is associated with arterial ammonia concentration and is useful for the evaluation of overt HE; however, controversy exists as to whether these neurophysiological methods are as sensitive as psychometric tests [16]. Cirrhotic patients with minimal HE should be considered as potential candidates for overt HE patients in need of therapeutic procedures [21]. Hyponatremia is a frequent

complication of advanced cirrhosis and is associated with increased morbidity and mortality; it may affect brain function and predispose subjects to HE [22], but its influence on minimal HE remains unclear. As hyponatremia was a risk factor for HE in a prospective study [23], the improvement of serum sodium concentration by the administration of vaptans could be considered in such cases.

54.4 Diagnostic Tools and Criteria

A thorough approach to determine the neuropsychiatric status in a cirrhotic patient would need to include the following: (1) an enquiry seeking evidence of change in the activities of daily living, (2) an enquiry seeking evidence of change in the activities of the memory, (3) an assessment of mental state utilizing the modified West Haven criteria, and (4) a comprehensive neurological examination looking particularly for evidence of subtle motor abnormalities [20].

However, these procedures are too complicated to be suitable for daily use. For this reason, physicians usually diagnose HE by combining the following methods: (1) quantitative neuropsychological tests, e.g., Wechsler Adult intelligence scale, number connection test (NCT), and reaction time to either visual or sound stimulus; (2) electrophysiological tests, e.g., electroencephalogram, cerebral evoked potential (both auditory and visual), critical flicker frequency, and event-related potential (P300); and (3) noninvasive brain function tests, e.g., MRI and positron emission tomography. In these methods, NCT is most widely used for the purpose of psychometric assessment in patients with liver cirrhosis. Thirty seconds are enough to complete this test for healthy individuals, but more than 50 s is necessary for patients with hepatic encephalopathy.

Kato et al. [18] have established normal values in healthy Japanese subjects and determined differences between healthy persons and persons with liver cirrhosis without clinical encephalopathy in a multicenter clinical trial. The test system, called the neuropsychological test, consists of eight tests: NCT A and B, a figure position test, a digit symbol test, a block design test, and reaction time tests A, B, and C. These results were affected by age, but not by gender or facility. The system was simplified so that two-dimensional operations using a computer were possible. All tests can be completed in about 20 min, including the time needed for practice and operation guide.

References

1. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715–35.

2. Tenorio-Laranga J, Montoliu C, Urios A, Hernandez-Rabaza V, Ahabrach H, Garcia-Horsman JA, Felipo V. The expression levels of prolyl oligopeptidase responds not only to neuroinflammation but also to systemic inflammation upon liver failure in rat models and cirrhotic patients. J Neuroinflammation. 2015;12:183.
3. Shawcross DL, Davies NA, Williams R, Jalan R. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. J Hepatol. 2004;40:247–54.
4. Butterworth RF. Hepatic encephalopathy: a central neuroinflammatory disorder? Hepatology. 2011;53:1372–6.
5. Bosoi CR, Tremblay M, Rose CF. Induction of systemic oxidative stress leads to brain oedema in portacaval shunted rats. Liver Int. 2014;34:1322–9.
6. Ahluwalia V, Wade JB, Thacker L, Kraft KA, Sterling RK, Stravitz RT, Fuchs M, Bouneva I, Puri P, Luketic V, Sanyal AJ, Gilles H, Heuman DM, Bajaj JS. Differential impact of hyponatremia and hepatic encephalopathy on health-related quality of life and brain metabolite abnormalities in cirrhosis. J Hepatol. 2013;59:467–73. https://doi.org/10.1016/j.jhep.2013.04.023.
7. Cash WJ, McConville P, McDermott E, McCormick PA, Callender ME, McDougall NI. Current concepts in the assessment and treatment of hepatic encephalopathy. QJM. 2010;103:9–16. https://doi.org/10.1093/qjmed/hcp152.
8. Das K, Singh P, Chawla Y, Duseja A, Dhiman RK, Suri S. Magnetic resonance imaging of brain in patients with cirrhotic and non-cirrhotic portal hypertension. Dig Dis Sci. 2008;53:2793–8.
9. Zhao HY, Wang HJ, Zhi LU, Zhen XU. Intestinal microflora in patients with liver cirrhosis. Chin J Dig. 2004;5:64–7.
10. Bajaj JS, Betrapally NS, Gillevet PM. Decompensated cirrhosis and microbiome interpretation. Nature. 2015;525:E1–2. https://doi.org/10.1038/nature14851.
11. Kang DJ, Betrapally NS, Ghosh SA, Sartor RB, Hylemon PB, Gillevet PM, Sanyal AJ, Heuman DM, Carl D, Zhou H, Liu R, Wang X, Yang J, Jiao C, Herzog J, Lippman HR, Sikaroodi M, Brown RR, Bajaj JS. Gut microbiota drive the development of neuroinflammatory response in cirrhosis in mice. Hepatology. 2016;64(4):1232–48. https://doi.org/10.1002/hep.28696.
12. Nicoletti V, Gioia S, Lucatelli P, Nardelli S, Pasquale C, Nogas Sobrinho S, Pentassuglio I, Greco F, De Santis A, Merli M, Riggio O. Hepatic encephalopathy in patients with non-cirrhotic portal hypertension: description, prevalence and risk factors. Dig Liver Dis. 2016;48(9):1072–7. https://doi.org/10.1016/j.dld.2016.06.014.
13. Kasagi Y, Saeki H, Akahoshi T, Kawasaki J, Ando K, Oki E, Ohga T, Tomikawa M, Kakeji Y, Shirabe K, Maehara Y. Non-cirrhotic portal-systemic encephalopathy caused by enlargement of a splenorenal shunt after pancreaticoduodenectomy for locally advanced duodenal cancer: report of a case. Surg Today. 2014;44:1573–6. https://doi.org/10.1007/s00595-013-0679-1.
14. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35:716–21.
15. Stojanov DB, Stojanov D. Minimal hepatic encephalopathy (MHE). In: Tanasescu R, editor. Miscellanea on encephalopathies—a second look. Rijeka, Croatia: Intech; 2012. p. 1–22.
16. Quero JC, Hartmann IJ, Meulstee J, Hop WC, Schalm SW. The diagnosis of subclinical hepatic encephalopathy in patients with cirrhosis using neuropsychological tests and automated electroencephalogram analysis. Hepatology. 1996;24:556–60.
17. Kato A, Tanaka H, Kawaguchi T, Kanazawa H, Iwasa M, Sakaida I, Moriwaki H, Murawaki Y, Suzuki K, Okita K. Nutritional management contributes to improvement in minimal hepatic encephalopathy and quality of life in patients with liver cirrhosis: a preliminary, prospective, open-label study. Hepatol Res. 2013;43:452–8.
18. Kato A, Kato M, Ishii H, Ichimiya Y, Suzuki K, Kawasaki H, Yamamoto SI, Kumashiro R, Yamamoto K, Kawamura N, Hayashi N, Matsuzaki S, Terano A, Okita K, Watanabe A. Development of quantitative neuropsychological tests for diagnosis of subclinical hepatic encephalopathy in liver cirrhosis patients and establishment of diagnostic criteria-multicenter collaborative study in Japanese. Hepatol Res. 2004;30:71–8.

19. Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. A controlled, double-blind clinical trial. Am J Dig Dis. 1978;23:398–406.
20. Amodio P, Montagnese S, Gatta A, Morgan MY. Characteristics of minimal hepatic encephalopathy. Metab Brain Dis. 2004;19:253–67.
21. Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, Rodés J. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol. 1999;30:890–5.
22. Ginès P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. Hepatology. 2008;48:1002–10. https://doi.org/10.1002/hep.22418.
23. Guevara M, Baccaro ME, Torre A, Gómez-Ansón B, Ríos J, Torres F, Rami L, Monté-Rubio GC, Martín-Llahí M, Arroyo V, Ginès P. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. Am J Gastroenterol. 2009;104:1382–9. https://doi.org/10.1038/ajg.2009.293.

Chapter 55
Treatment of Hepatic Encephalopathy

Kosuke Kaji, Norihisa Nishimura, Kei Moriya, and Hitoshi Yoshiji

Abstract Hepatic encephalopathy (HE) is predominantly induced by a portosystemic shunt as a complication of excessive portal hypertension. Initial treatments for HE involve the identification and improvement of the causal triggers, such as infection, constipation, dehydration, and gastrointestinal bleeding. A majority of the pharmacotherapies are aimed at decreasing the production of ammonia. Lactulose alters gastrointestinal pH by favoring lactobacilli over urease-containing bacteria and enhances the production of nonabsorbable ammonia. Furthermore, these laxatives enhance fecal nitrogen excretion. Although neomycin was the first antibiotic to be effective in the treatment of HE, its use has been limited because of ototoxicity and nephrotoxicity. Recently, rifaximin, a minimally absorbable oral antibiotic, which is available in many countries, has been used in lactulose resistance encephalopathy. When used in conjunction with lactulose, rifaximin has been shown to reduce recurrent encephalopathy and hospitalization. Supplementation of branched-chain amino acids is also beneficial for patients with HE because of their stimulatory effect on ammonia detoxification to glutamine. Balloon-occluded retrograde transvenous obliteration is recommended for patients with refractory HE especially caused by portosystemic shunt. Liver transplantation is eventually performed in patients who are resistant to the abovementioned pharmacological and interventional therapies.

Keywords Lactulose · Rifaximin · BCAAs · B-RTO

55.1 Introduction

Hepatic encephalopathy (HE) is a spectrum of neuropsychiatric syndromes and can cause major complications in patients with acute and chronic liver failures due to portosystemic shunting [1]. It is characterized by a wide range of changes in mental

K. Kaji (✉) · N. Nishimura · K. Moriya · H. Yoshiji
Division of Gastroenterology and Hepatology, Third Department of Internal Medicine, Nara Medical University, Kashihara, Nara, Japan
e-mail: kajik@naramed-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_55

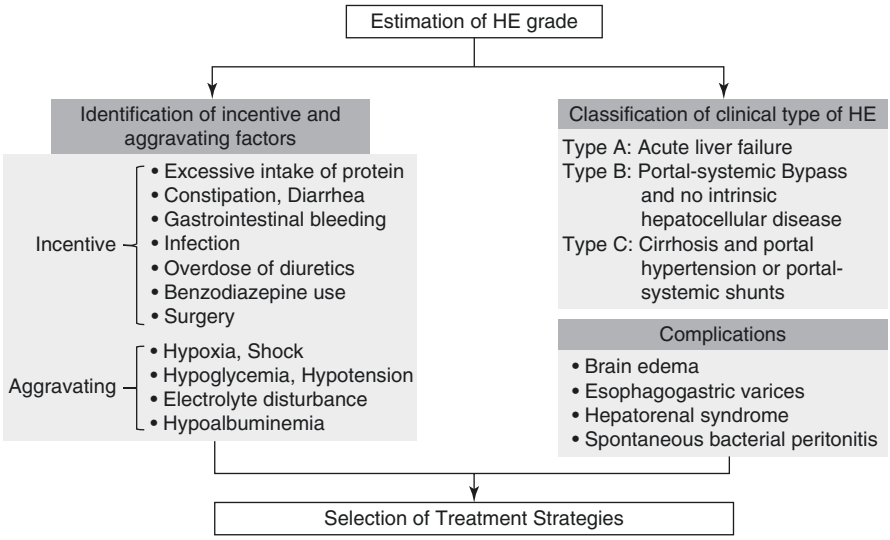


Fig. 55.1 First step for HE management is to estimate HE grade. Initial treatments for HE involve the identification of the causal triggers and complications and the classification of clinical type

state starting from minimal signs of altered brain function to deep coma. HE is generally managed depending on its type and severity; many patients with covert HE may not require treatment unless the condition is thought to adversely affect their quality of life [2]. Episodes of overt HE can be shortened with appropriate treatment, thereby preventing the occurrence of any further events (Fig. 55.1) [3]. This chapter reviews the established and recently developed treatments for patients with HE.

55.2 Removal of Incentives and Proper Nutrition

The first step in the treatment of overt HE is to identify the cause of the disease. Previous reports have demonstrated that 70% of the patients with overt HE presented with underlying causes, such as excessive consumption of dietary protein, gastrointestinal bleeding, diarrhea, constipation, vomiting, infection, surgery, electrolyte disturbance, and dehydration due to overdose of diuretics and benzodiazepine use [1, 2]. Hence, the removal of these causal triggers contributes to the success of the treatment in patients with HE (Fig. 55.2).

Protein-restricted diets have been advised for these patients on account of reduced intestinal ammonia production. However, current guidelines do not propose protein restriction for the long-term management of cirrhotic patients because it may enhance protein breakdown and worsen the prognosis of cirrhosis [3, 4]. Thus, an intake of 1.2–1.5 g/kg of proteins in small meals distributed throughout the day, with a late evening snack (LES) of complex carbohydrates, is recommended [5].

1. Removal and prevention of incentive and aggravating factors
2. Maintain protein intake of 1.0–1.5 g/kg daily, over 4–6 meals daily with LES
3. Oral BCAA supplementation
4. Non absorbable disaccharides Lactulose: 30–90 ml per os/per anum 3 to 4 times daily Lactitol: 18–36 g per os 3 to 4 times daily
5. Minimally absorbed antibiotics Neomycin: 1g per os 2 to 4 times daily Rifaximin: 550 mg per os twice daily
6. Intravenous administration of BCAAs during coma period
7. B-RTO may be considered for severe HE with portosystemic shunt
8. Liver transplantation for appropriate candidates

Fig. 55.2 Therapeutic strategies for overt persistent HE

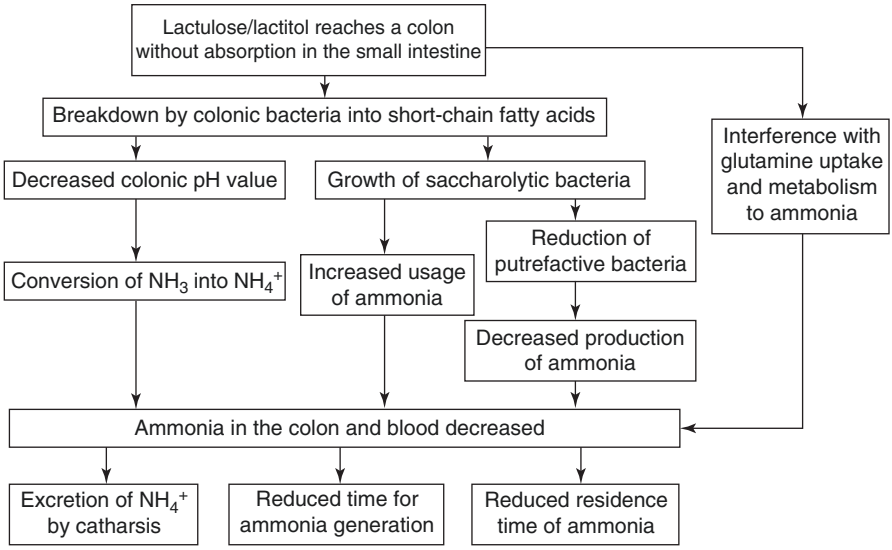


Fig. 55.3 Nonabsorbable disaccharides reduce ammonia in the colon and blood with multiple steps

55.3 Pharmacological Treatments

55.3.1 Nonabsorbable Disaccharides

Current pharmacological therapies for HE mainly aim at the reduction of ammonia because of general consensus that the gut-derived neurotoxin ammonia plays a key role in this disease (Fig. 55.3) [6]. Nonabsorbable disaccharides have been developed as the first-line treatment to lower the intestinal production and absorption of ammonia via several potential mechanisms. First, disaccharides are metabolized to acetic and lactic acids by the bacteria in the colon, leading to a promoted catharsis

caused by an increase in intraluminal gas formation and osmolality and a reduction in intraluminal pH [6, 7]. These cathartic effects also cause a fourfold increase in fecal nitrogen excretion. Second, the colonic metabolism of nonabsorbable disaccharides creates a hostile environment for the survival of intestinal bacteria with urease activity involved in the production of ammonia [6, 7]. Additionally, nonabsorbable disaccharides inhibit glutaminase activity and interfere with the intestinal uptake of glutamine and its subsequent metabolism to ammonia [8].

Lactulose, a synthetic disaccharide, is the most commonly utilized nonabsorbable disaccharide in patients with HE. Similarly, lactitol (p-galactosido-sorbitol) is also clinically available as a disaccharide analog of lactulose, which is neither absorbed nor broken down in the small intestine.

The daily mean doses of lactulose ranged from 30 ml to 90 ml in order to obtain two to three semisoft stools per day (Fig. 55.2) [2]. The median duration of treatment was 15 days (range, 5–360 days). Lactitol has also been used for the treatment of HE; a meta-analysis has shown no statistical differences in the percentage of improved patients after lactitol or lactulose intake, whereas a slightly higher frequency of flatulence has been reported in patients treated with lactulose when compared with those treated with lactitol [9].

The recently updated 2016 systematic Cochrane Review on the efficacy and safety of nonabsorbable disaccharides demonstrates the significantly beneficial effect of these agents on HE, both minimal and overt, and their overall beneficial effect on liver-related morbidity [10].

55.3.2 Minimally Absorbed Antibiotics

Antimicrobials diminish bacterial production of ammonia and other bacteria-derived toxins via suppression of the intestinal flora. In Japan, neomycin is the most commonly used antimicrobial as an alternative treatment for patients with HE, who are intolerant or unresponsive to nonabsorbable disaccharides. Neomycin has been reported to be as effective as lactulose, whereas a randomized, double-blind, controlled trial comparing neomycin versus placebo in acute HE showed no significant difference in symptomatic improvement [11]. Additionally, the adverse effects of this drug frequently restrict its use as a first-line pharmacological agent. Although poorly absorbed, systemic exposure to neomycin in excessive amounts induces hearing loss and renal toxicity, indicating that long-term neomycin therapy requires annual auditory testing and continuous monitoring of the renal function.

Rifaximin is a newly developed oral antibiotic with broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative bacteria [12]. It has minimal systemic absorption at less than 1% and a low risk for inducing resistance in patients. Several clinical trials have compared rifaximin to disaccharides, lactulose, and lactitol and also to the antimicrobial neomycin. Over a 6-month period, rifaximin was more effective in maintaining remission from HE when compared with a placebo (Fig. 55.4) [13]. Moreover, a driving simulator performance

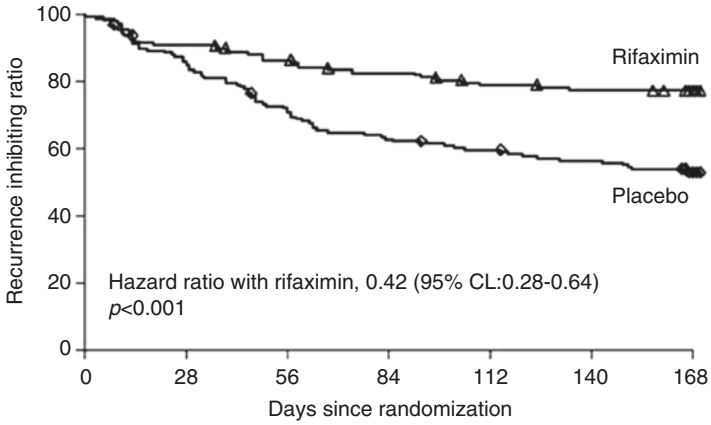


Fig. 55.4 Rifaximin prevents a breakthrough episode of overt HE (From Bass NM et al. [13])

is significantly improved in patients with minimal HE after treatment with rifaximin when compared with placebo [14]. A meta-analysis has shown that rifaximin appears to be beneficial in terms of the fewer number of adverse effects caused by the drug owing to its limited systemic absorption [15]. A randomized controlled trial (RCT) conducted by Sharma et al. demonstrated the effectiveness of the combination of lactulose and rifaximin (higher recovery from HE and lower mortality) when compared with lactulose alone for the treatment of overt HE [16]. Another recent meta-analysis illustrated that rifaximin played a positive role in the secondary prevention of HE; it was also shown to be beneficial in increasing the proportion of patients who recovered from HE and reducing mortality [17].

55.3.3 Branched-Chain Amino Acids

Patients with cirrhosis have a lower concentration of the essential branched-chain amino acids (BCAAs), leucine, isoleucine, and valine. Nutritional supplementations with BCAAs have been assessed as a treatment option for cirrhosis and HE. The action of BCAAs was addressed on the false neurotransmitter hypothesis, which suggests that imbalance in blood amino acids induces an increased efflux of cerebral aromatic amino acids with the subsequent generation of false neurotransmitters. Recent research shows that BCAAs also play an important role in muscle metabolism, with glutamine production from ammonia fixation and inhibition of proteolysis [18]. A meta-analysis of seven RCTs showed an improvement in the mental state induced by a BCAA-enriched amino acid solution, and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on parental nutrition have recommended this solution for patients with grade III–IV HE [4]. A recent meta-analysis involving eight trials of orally administered BCAA supplements and seven trials of intravenously administered BCAAs also indicated their beneficial effects on HE [19].

On the other hand, a bolus dose of BCAAs results in an immediate increase in ammonia concentrations. These complex mechanisms and the clinical differences between patients with acute or recurrent HE may underlie the difficulty in assessing the clinical effects of BCAAs. Therefore, additional RCTs are required to determine the effect of BCAAs when compared with other interventions, such as nonabsorbable disaccharides, rifaximin, and other antibiotics.

55.3.4 Other Drugs

55.3.4.1 Zinc Preparation

Zinc is a critical cofactor involved in the reactions of ammonia metabolism- related enzymes, including ornithine transcarbamylase, which converts ammonia to urea, and glutamine synthetase, which metabolizes ammonia to glutamic acid. Animal models have shown that zinc deficiency decreases the activity of ornithine transcarbamylase, whereas zinc supplementation markedly increases hepatic ornithine transcarbamylase activity [20]. Zinc deficiency has also been reported to impair the activity of muscle glutamine synthetase, which leads to hyperammonemia [21]. In clinical practice, zinc deficiency is frequently observed in patients with cirrhosis and HE, and short-term oral zinc supplementation may improve HE by converting ammonia to urea, consequently improving the health-related quality of life [21].

55.3.4.2 L-Carnitine

L-Carnitine is a vitamin-like substance involved in lipid metabolism and is associated with the translocation of acetyl-CoA into the mitochondria, the promotion of the metabolic flux in the tricarboxylic acid cycle by sparing free CoA and activating the transport of adenine nucleotides across the inner mitochondrial membrane, and the prevention of pyruvate dehydrogenase inhibition by adenylate translocase [22]. Recent report has described the beneficial effect of L-carnitine supplementation on HE [23]. In Japan, L-carnitine supplementation is recommended for patients with carnitine deficiency [3]. However, interestingly, a recent study has shown that L-carnitine supplementation improves refractory hyperammonemia in cirrhotic patients, even though serum levels of carnitine were similar to those in healthy individuals [23]. Further investigations are required to determine the indications for L-carnitine supplementation in cirrhotic patients with refractory hyperammonemia.

55.4 Artificial Liver Support

Artificial devices have been shown to improve HE symptoms in patients with decompensated cirrhosis, probably by favoring the disposal of toxins accumulated as a result of liver failure. The currently available artificial liver support systems are

based on the principle of blood purification by albumin dialysis or by plasma separation and filtration. Extracorporeal albumin dialysis (ECAD), using the molecular adsorbent recirculating system, has been recently evaluated in a RCT. Seventy patients with grade III or grade IV HE were randomized to receive standard medical therapy (SMT) with or without ECAD. Significantly frequent and faster improvements in HE were observed in patients who received ECAD with SMT when compared with those who received SMT alone [24]. These findings indicate the availability of albumin dialysis as a bridge to transplantation.

55.5 Balloon-Occluded Retrograde Transvenous Obliteration

Balloon-occluded retrograde transvenous obliteration (B-RTO) has been utilized as the first-line treatment for the prevention of fatal bleeding from solitary gastric varices [25]. During B-RTO treatment, obliteration of the gastric varices results in the occlusion of the splenorenal shunt, leading to modifications in portal hemodynamics. A progressed portosystemic shunt also develops severe HE, as well as gastric varices, in some patients with cirrhosis. Thus, a hemodynamic modification by B-RTO is reportedly effective for chronic recurrent HE especially due to the portosystemic shunt [26]. Several noncontrolled case series have shown that the occlusion of the large portosystemic shunt by B-RTO relieves HE [26, 27]. B-RTO is also reported to augment portal venous blood flow and improve liver function test findings [28]. An elevated hepatic venous pressure gradient after B-RTO is one aspect of the effect on liver function. Careful evaluation of portal hemodynamics is necessary in order to select patients B-RTO from the standpoints of the efficacy and safety. Based on these evidences, adequate evaluation and selection of patients with portosystemic HE have been proposed in Japan [3].

55.6 Liver Transplantation

The treatment for a hospitalized, severely ill cirrhotic patient with HE should be planned from a transplant perspective. Patients with severe multiple organ failure, including severe HE, can have beneficial outcomes with liver transplantation. Over 85% mortality was observed in patients with three or more organ failures, who had not undergone liver transplantation. This was reduced to a mortality of 20% in those with early liver transplantation [29]. However, at present, priority is not given to severe HE patients on the waiting list for transplantation, where organ allocation is based on the model for end-stage liver disease (MELD) score, which underestimates the risk of death [30]. A new scoring system has been developed and validated by the chronic liver failure (CLIF) consortium, which needs further evaluation before it can be implemented for the clinical allocation of organs.

References

1. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35(3):716–21.
2. American Association for the Study of Liver D, European Association for the Study of the L. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol. 2014;61(3):642–59.
3. Fukui H, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51(7):629–50.
4. Plauth M, Cabre E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al. ESPEN guidelines on enteral nutrition: liver disease. Clin Nutr. 2006;25(2):285–94.
5. Okita M. Chronic hepatic disease and dietary instruction. Hepatol Res. 2004;30S:92–5.
6. Patel VC, White H, Stoy S, Bajaj JS, Shawcross DL. Clinical science workshop: targeting the gut-liver-brain axis. Metab Brain Dis. 2016;31(6):1327–37.
7. Weber FL Jr, Banwell JG, Fresard KM, Cummings JH. Nitrogen in fecal bacterial, fiber, and soluble fractions of patients with cirrhosis: effects of lactulose and lactulose plus neomycin. J Lab Clin Med. 1987;110(3):259–63.
8. van Leeuwen PA, van Berlo CL, Soeters PB. New mode of action for lactulose. Lancet. 1988;1(8575–6):55–6.
9. Blanc P, Daures JP, Rouillon JM, Peray P, Pierrugues R, Larrey D, et al. Lactitol or lactulose in the treatment of chronic hepatic encephalopathy: results of a meta-analysis. Hepatology. 1992;15(2):222–8.
10. Gluud LL, Vilstrup H, Morgan MY. Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. Cochrane Database Syst Rev. 2016;4:CD003044.
11. Strauss E, Tramote R, Silva EP, Caly WR, Honain NZ, Maffei RA, et al. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepato-gastroenterology. 1992;39(6):542–5.
12. Jiang ZD, DuPont HL. Rifaximin: in vitro and in vivo antibacterial activity—a review. Chemotherapy. 2005;51(Suppl 1):67–72.
13. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362(12):1071–81.
14. Bajaj JS, Heuman DM, Wade JB, Gibson DP, Saeian K, Wegelin JA, et al. Rifaximin improves driving simulator performance in a randomized trial of patients with minimal hepatic encephalopathy. Gastroenterology. 2011;140(2):478–87.e1.
15. Eltawil KM, Laryea M, Peltekian K, Molinari M. Rifaximin vs. conventional oral therapy for hepatic encephalopathy: a meta-analysis. World J Gastroenterol. 2012;18(8):767–77.
16. Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. Am J Gastroenterol. 2013;108(9):1458–63.
17. Kimer N, Krag A, Moller S, Bendtsen F, Gluud LL. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. Aliment Pharmacol Ther. 2014;40(2):123–32.
18. Dam G, Ott P, Aagaard NK, Vilstrup H. Branched-chain amino acids and muscle ammonia detoxification in cirrhosis. Metab Brain Dis. 2013;28(2):217–20.
19. Gluud LL, Dam G, Les I, Cordoba J, Marchesini G, Borre M, et al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev. 2015;2:CD001939.
20. Riggio O, Merli M, Capocaccia L, Caschera M, Zullo A, Pinto G, et al. Zinc supplementation reduces blood ammonia and increases liver ornithine transcarbamylase activity in experimental cirrhosis. Hepatology. 1992;16(3):785–9.

21. Yoshida Y, Higashi T, Nouso K, Nakatsukasa H, Nakamura SI, Watanabe A, et al. Effects of zinc deficiency/zinc supplementation on ammonia metabolism in patients with decompensated liver cirrhosis. Acta Med Okayama. 2001;55(6):349–55.
22. Krahenbuhl S, Reichen J. Carnitine metabolism in patients with chronic liver disease. Hepatology. 1997;25(1):148–53.
23. Shiraki M, Shimizu M, Moriwaki H, Okita K, Koike K. The carnitine dynamics and their effects on hyperammonemia in cirrhotic Japanese patients. Hepatol Res. 2017;47(4):321–7.
24. Hassanein TI, Tofteng F, Brown RS Jr, McGuire B, Lynch P, Mehta R, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology. 2007;46(6):1853–62.
25. Kanagawa H, Mima S, Kouyama H, Gotoh K, Uchida T, Okuda K. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. J Gastroenterol Hepatol. 1996;11(1):51–8.
26. Kato T, Uematsu T, Nishigaki Y, Sugihara J, Tomita E, Moriwaki H. Therapeutic effect of balloon-occluded retrograde transvenous obliteration on portal-systemic encephalopathy in patients with liver cirrhosis. Intern Med. 2001;40(8):688–91.
27. Ohmoto K, Miyake I, Tsuduki M, Ohno S, Yamamoto S. Control of solitary gastric fundal varices and portosystemic encephalopathy accompanying liver cirrhosis by balloon-occluded retrograde transvenous obliteration (B-RTO): a case report. Hepato-Gastroenterology. 1999;46(26):1249–52.
28. Uehara H, Akahoshi T, Tomikawa M, Kinjo N, Hashimoto N, Nagao Y, et al. Prediction of improved liver function after balloon-occluded retrograde transvenous obliteration: relation to hepatic vein pressure gradient. J Gastroenterol Hepatol. 2012;27(1):137–41.
29. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426–37, 37.e1–9.
30. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60(2):715–35.

Chapter 56
[Column] Portosystemic Shuntopathy: This Column Is the Postscript to Chap. 5

Atsushi Toyonaga

Portosystemic shunts including esophagogastric varices are formed in patients with portal hypertension. Esophageal varices do not serve as major shunts, while isolated gastric fundal varices (IGFVs) become major splenorenal shunts. A major shunt is particularly large and has a high shunt ratio. A major splenorenal shunt causes various disease states including classic portosystemic encephalopathy, in other words recurrent hepatic encephalopathy. Although a portosystemic shunt develops as a biological adaptation, excessive portal steal results in liver failure or variceal rupture/bleeding and significantly worsens the prognosis.

Markedly increased portal steal blood in a splenorenal shunt flows into IGFVs via the splenic vein, a part of the portal system. Then, the blood enters the systemic circulation through the left renal vein. IGFVs that are formed in the middle of the splenorenal shunt and are likely to bleed cannot be controlled easily because they are resistant to endoscopic treatment. Balloon-occluded retrograde transvenous obliteration (B-RTO) was introduced as a radical treatment for IGFVs [1]. B-RTO enables not only ablation of IGFVs [2] but also occlusion/ablation of a major splenorenal shunt. Moreover, this technique is remarkably effective in treating portosystemic encephalopathy [3, 4]. Once the therapeutic procedure has been completed successfully, the probability of recurrence is negligible.

Portosystemic shuntopathy or portosystemic shunt syndrome is a generic term for various pathological conditions caused by portal steal blood flow in a major shunt. These pathological conditions include the following:

1. Recurrent hepatic encephalopathy
2. Decreased hepatic reserve
3. Abnormal glucose tolerance
4. Endotoxemia

A. Toyonaga
Kurume University, Yasumoto Hospital, Kurume, Fukuoka, Japan
e-mail: atsushi-toyonaga@w3.dion.ne.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_56

5. Hormonal dysfunction
6. Shortened survival
7. Others

As demonstrated by accumulated cases, portosystemic shuntopathy can be improved by B-RTO. The fact that B-RTO improves decreased hepatic reserve [5–9] strongly supports the conventionally proposed intact hepatocyte theory [10–12], which postulates that residual hepatocytes remain functionally normal in liver cirrhosis, in comparison with normal hepatocytes. There is uneven distribution of blood flow in the liver due to shunt and nodule formation and fibrosis at the level of liver microcirculation.

Therefore, even if hepatocytes themselves have no organic abnormality, hepatocytes that cause a functional abnormality are produced due to insufficient blood flow. B-RTO occludes the major shunt, and the portal blood flow is restored. In this manner, functionally abnormal hepatocytes are likely to improve. This benefit (prevention of exacerbation) continues to be effective for at least 3 years [9].

The author believed that portosystemic shuntopathy was a proper expression and submitted his paper with this expression to an international peer-reviewed journal. However, the reviewer stated that the term "shuntopathy" was inappropriate. At that time, the author was not sure what term he should use and replaced portosystemic shuntopathy with portosystemic shunt syndrome.

There are many medical terms having "pathy" as a suffix, such as gastropathy, neuropathy, enteropathy, myopathy, nephropathy, etc. The author investigated these terms and found that they combined the name of an organ and "pathy." Accordingly, he speculated that a combination of shunt and pathy was probably unacceptable because shunt indicated a medical condition rather than an organ. Although he used portosystemic shunt syndrome in a paper submitted to an international journal, portosystemic shuntopathy still attracts his sympathy. The author understands that portosystemic shuntopathy may be incorrect from the viewpoint of medical terminology and that portosystemic shunt syndrome rather than portosystemic shuntopathy will be used by an increasing number of researchers [9].

References

1. Kanagawa H, Mima S, Kouyama H, et al. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. J Gastroenterol Hepatol. 1996;11:51–8.
2. Emori K, Toyonaga A, Oho K, et al. Balloon-occluded retrograde transvenous obliteration versus endoscopic injection sclerotherapy for isolated gastric varices: a comparative study. Kurume Med J. 2013;60:105–13.
3. Kato T, Umematsu T, Nishigaki Y, et al. Therapeutic effect of balloon-occluded retrograde transvenous obliteration on portal systemic encephalopathy in patients with liver cirrhosis. Intern Med. 2001;40:688–91.
4. Akahoshi T, Hashizume M, Tomikawa M, et al. Long term results of balloon-occluded retrograde transvenous obliteration for gastric variceal bleeding and risky gastric varices: a 10-year experience. J Gastroenterol Hepatol. 2008;23:1702–9.

5. Akahane T, Iwasaki T, Kobayashi N, et al. Changes in liver function parameters after occlusion of gastrorenal shunts with balloon-occluded retrograde transvenous obliteration. Am J Gastroenterol. 1997;92:1026–30.
6. Fukuda T, Hirota S, Sugimura K. Long term results of balloon-occluded retrograde transvenous obliteration for treatment of gastric varices and hepatic encephalopathy. J Vas Interv Radiol. 2001;12:327–36.
7. Miyamoto Y, Oho K, Kumamoto M, et al. Balloon-occluded retrograde transvenous obliteration improves liver function in patients with cirrhosis and portal hypertension. J Gastroenterol Hepatol. 2003;18:934–42.
8. Ninoi T, Nishida N, Yamamoto Y, et al. Balloon-occluded retrograde transvenous obliteration of gastric varices with gastrorenal shunt : long term follow-up in 78 patients. Am J Roentogenol. 2005;184:1340–6.
9. Kumamoto M, Toyonaga A, Inoue H, et al. Long term results of balloon-occluded retrograde transvenous obliteration for gastric fundal varices: hepatic deterioration links to portosystemic shunt syndrome. J Gastroenterol Hepatol. 2010;25:1129–35.
10. Wood AJJ, Villeneuve JP, Branch RA, et al. Intact hepatocyte theory of impaired drug metabolism in experimental cirrhosis in rat. Gastroenterology. 1979;76:1358–62.
11. Kawasaki S, Imamura H, Idezuki Y, et al. Direct evidence for the intact hepatocyte theory in patients with liver cirrhosis. Gastroenterology. 1992;102:1351–5.
12. Cardoso JE, Gautreu C, Jeyaraj PR, et al. Augmentation of portal blood flow improves function of human cirrhotic liver. Hepatology. 1994;19:375–80.

Part IX
Aberrant Portal Hemodynamics

Chapter 57
Idiopathic Portal Hypertension

Shoichi Matsutani

Abstract Idiopathic portal hypertension (IPH) is a disease presenting as non-cirrhotic portal hypertension due to a presinusoidal portal blood flow block and increased portal blood flow with an enlarged spleen, although the etiologic factors have not been identified. IPH is most common in middle-aged females and is predominant in females versus males in the overall population in Japan. The major signs and symptoms are pancytopenia with splenomegaly and gastroesophageal varices. The clinical manifestations are relatively mild and insidious in most of the patients, except in the case of variceal hemorrhage. A high incidence of portal vein thrombosis is also characteristic. Diagnosis is made by the differentiating IPH from the diseases of portal hypertension with identified causes because there are no specific clinical findings for the diagnosis of IPH. Portal and hepatic venography or liver histology is helpful for the diagnosis. The treatment of portal hypertension-related problems is the same as for problems related to liver cirrhosis. The clinical course and overall survival are well maintained in patients for whom gastroesophageal varices are effectively controlled. However, complications such as refractory ascites or intestinal ectopic varices may appear in the late stages of the disease.

Keywords Non-cirrhotic portal hypertension · Banti disease · Presinusoidal portal blood flow block · Portal vein thrombosis

57.1 Introduction

Idiopathic portal hypertension (IPH) is a disease presenting as non-cirrhotic portal hypertension without any evident causes [1]. The identification of this disease started in the late 1880s when Dr. Guido Banti at the University of Bologna reported on the "Banti disease" [2, 3]. Since then, studies have been conducted continuously,

S. Matsutani (✉)
Department of Gastroenterology, Funabashi Municipal Medical Center, Funabashi, Chiba, Japan
e-mail: matsu803@pg7.so-net.ne.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_57

and controversies around the world concerning the etiology and clinical entity of the disease have consequently resulted in various nominations for this disease, including primary portal hypertension [4], idiopathic presinusoidal portal hypertension [5], idiopathic tropical splenomegaly [6], non-cirrhotic portal fibrosis [7], hepatoportal sclerosis [8], and idiopathic non-cirrhotic portal hypertension [9, 10]. In Japan, studies of this disease have been conducted continuously since the 1970s under the Japanese Research Committee for the study of Portal Hemodynamic Abnormalities [1] (see annual reports of the Research Committee). Although this disease is seen worldwide, clinical manifestations are somewhat diverse between regions. In this chapter, we mainly focus on summarizing the clinical aspects of IPH in Japan.

57.2 Etiology

A blockage of presinusoidal portal blood flow and increased portal blood flow with an enlarged spleen are considered the causative factors for portal hypertension in IPH [1]. However, the etiologic factors for the pathological conditions in both the liver and the spleen have not yet been identified. The postulated etiological factors are listed as follows: infections, chemicals, immunological abnormalities, genetic factors, and thrombophilia. Among these factors, abnormal immunological processes are considered potential etiologic factors [11] according to clinical results showing a high incidence of autoantibodies in IPH patients and an overlap of IPH with various autoimmune diseases [12]. However, the direct mechanism of the development of portal hypertension by immunological abnormalities has not been elucidated. Animal studies showing that experimental periportal fibrosis is induced by chronic sensitization to intestinal bacteria suggest an association between the development of a presinusoidal portal blood flow block and chronic translocation of intestinal bacteria into the portal vein system [13, 14]. Recent research demonstrated that an increase in cytokines, such as TGF-β originating from an enlarged spleen, may cause fibrotic changes of portal vein branches and the portal area in the liver through endothelial mesenchymal transition [15, 16]. Furthermore, connective tissue growth factor, which may induce portal fibrosis, has been reported to be increased in IPH [17]. The increase in these fibrogenic cytokines is postulated as a potential cause of fibrotic changes in and around the peripheral portal veins in IPH.

57.3 Epidemiology

A national survey in Japan showed a gradual decrease in the incidence of IPH between 1985 and 2004 (annual reports from the Research Committee: 1400, 920, and 850 patients in 1985, 1998, and 2004, respectively) [18]. IPH is most common in middle-aged females (40–50 years of age), and the disease is predominant in females versus males in the overall population (male to female ratio, 1:3) in Japan.

This ratio is quite different from that in Western countries where there is a predominance of male patients. The median age of patients with IPH in Japan is 41.7 years old for male patients and 51.9 years old for female patients.

57.4 Pathophysiology

The liver pathology of IPH includes periportal fibrosis and narrowing or disappearance of small portal vein branches and leads to raised portal pressure by increasing the presinusoidal resistance of the portal blood flow (Fig. 57.1) [19]. Long-term decrease in portal perfusion and pathologic changes of the liver induce liver atrophy in the advanced stage of IPH. These changes are clinically represented by the narrowing or paucity of portal vein branches, as seen using direct portal venography (Fig. 57.2) [20], and a small difference between free and wedged hepatic vein pressure during hepatic venous catheterization [21]. A hepatic venogram of a liver with IPH shows a unique figure of hepatic vein with a "weeping willow" appearance and anastomoses between hepatic vein branches, which represent atrophic changes of the liver [22]. The lack of progression to cirrhosis in the IPH liver results in a relatively preserved liver function during the long-term course of IPH. A high incidence of portal vein thrombosis is characteristic of IPH in both Japanese and Western patients [23, 24]. However, the state of portal thrombosis is different between countries; more thrombophilic factors are present in Western patients [23] than in Japanese patients [25]. Portal vein thrombosis is associated with the worsening of the clinical course through hypoperfusion of the liver and progress of portal hypertension. Splenomegaly with hypersplenism, which often appears at an early stage, is another characteristic sign of IPH [26]. Pathology of the spleen in IPH includes a dilated splenic sinus that differs from congestive splenomegaly seen in liver cirrhosis. It is postulated that patients with IPH have an actively enlarged spleen with increased portal blood flow [26] and pancytopenia in the peripheral blood.

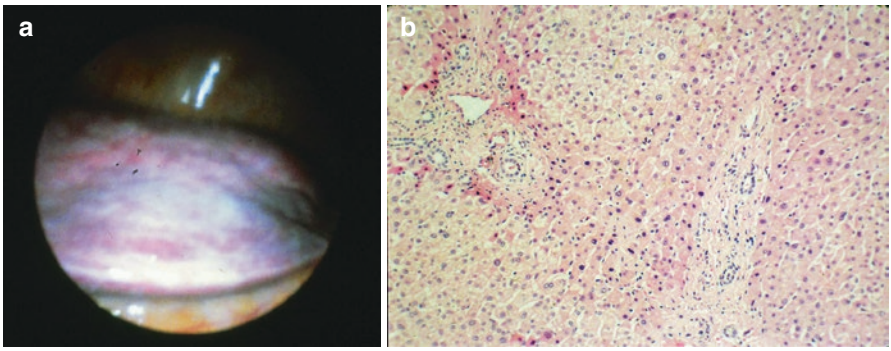


Fig. 57.1 Pathology of the liver in IPH patient. (**a**) Laparoscopic image. The surface of the liver is wavelike with undulation. (**b**) Histology. The portal vein shows destruction and narrowing with fibrotic changes in the portal area

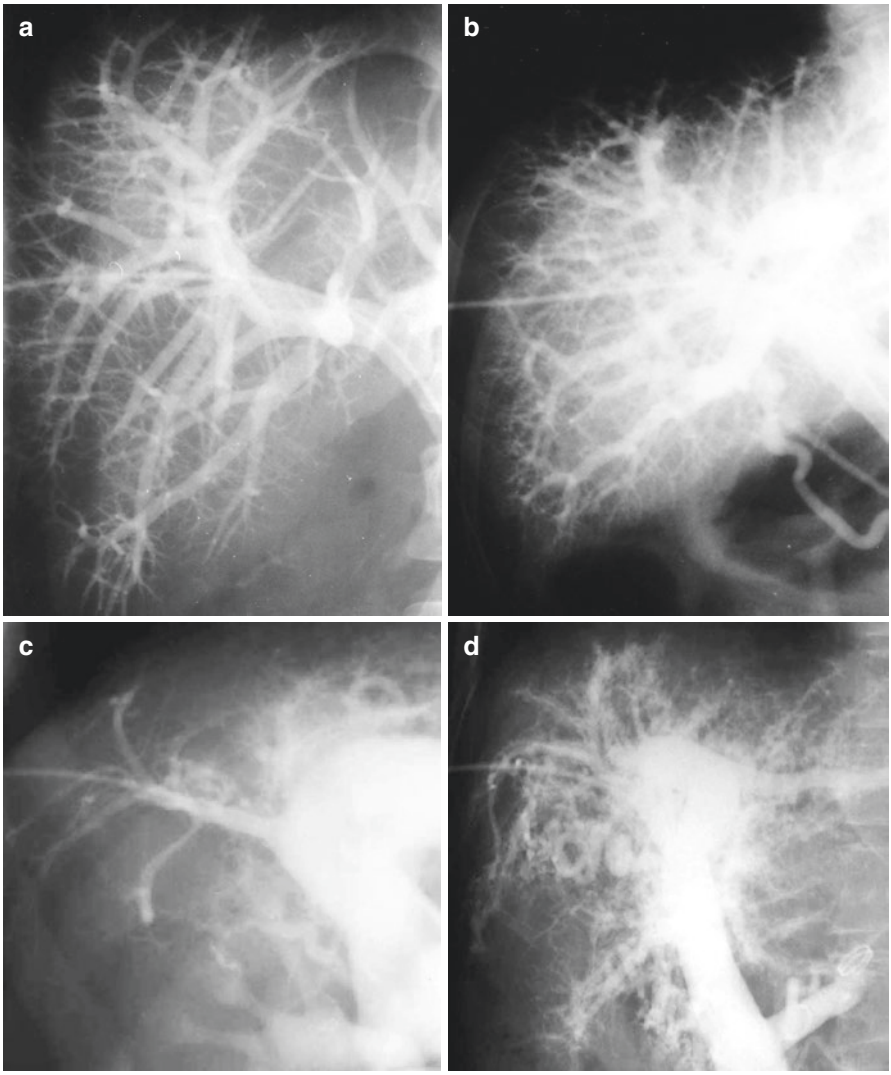


Fig. 57.2 Angiographic images of the portal vein in the liver in controls and in IPH patients. (**a**) Non-liver disease without portal hypertension. Portal vein branches divide symmetrically and regularly taper. (**b**) Liver cirrhosis. Portal vein branches are slightly winding and distorted. However, the peripheral branches are opacified almost regularly. (**c**) IPH. Opacification of portal vein branches is significantly poor in the right portal vein. (**d**) IPH. Portal vein branches show neovasculatures of fine and hazy vessels without regular division and tapering

57.5 Clinical Aspects

57.5.1 Clinical Manifestations

The major signs and symptoms of IPH are pancytopenia with splenomegaly and gastroesophageal varices with or without gastrointestinal bleeding. In addition, anemia, thrombocytopenia, and an enlarged spleen are common clinical manifestations that are often clues to the diagnosis of IPH. The clinical manifestations are relatively mild and insidious in most of the patients, except in the case of variceal hemorrhage. Overall, liver function is well preserved during the long-term course of disease. However, the serum albumin level, which is associated with liver cell function, and platelet count tend to decrease at the advanced stage, even in cases without overt hepatic failure. The clinical characteristics in recent Japanese IPH patients are summarized in Tables 57.1 and 57.2.

Table 57.1 Clinical findings at diagnosis and changes during follow-up in Japanese IPH patients (1987–2016, Chiba)

		End of follow-up	
	Initial findings	Alive	Dead[a]
	(*n* = 31)	(*n* = 25)	(*n* = 6)
Duration of follow-up (years)[b]		21.0 ± 9.3	16.1 ± 9.0
Age (years)[b]	52.2 ± 14.1	72.3 ± 9.9	71.7 ± 9.9
Variceal hemorrhage (*n*)	11 (35.5%)	2 (8.0%)	0
Ascites (*n*)	0	6 (24.0%)	4 (66.7%)
Refractory (*n*)		2	4
Portal vein thrombosis (*n*)	7 (22.6%)	15 (60.0%)	5 (83.3%)
Hepatic encephalopathy (*n*)	1 (3.2%)	2 (8.0%)	0

[a]Causes of death: infections 2, refractory ascites 2, undetermined 2
[b]Mean±SD

Table 57.2 Laboratory findings at diagnosis and changes during follow-up in Japanese IPH patients (1987–2016, Chiba)

		Follow-up	
	At diagnosis	Alive	Dead
Hemoglobin	11.5 ± 2.3	12.5 ± 1.5	11.1 ± 2.9
White blood cell count	3700 ± 1400	3900 ± 1800	5200 ± 300
Platelet count	9.8 ± 6.7	9.6 ± 5.7	6.8 ± 2.9
Total bilirubin	1.4 ± 0.7	1.7 ± 1.1	1.4 ± 0.5
Albumin	3.9 ± 0.5	3.7 ± 0.4	3.4 ± 0.5
Prothrombin	80 ± 21	78 ± 19	84 ± 23

Hemoglobin: g/dL, White blood cell count: /μL, Platelet count: $\times 10^4$/μL
Total bilirubin: mg/dL, Albumin: g/dL, Prothrombin: %, Mean±SD

57.5.2 Diagnosis

There are unfortunately no specific signs, symptoms, laboratory data, imaging, or histology examinations to diagnose IPH. When a case of non-cirrhotic portal hypertension is suspected during routine clinical examinations, including imaging diagnosis (Fig. 57.3), ultrasound elastography is useful to diagnose non-cirrhotic conditions of the liver noninvasively [27]. A patient presenting with portal hypertension and well-preserved liver functions; the absence of causative factors for liver cirrhosis, including hepatitis viral markers, significant alcohol consumption, or liver disease-specific immunological markers; or the lack of clinical findings indicating miscellaneous causes of non-cirrhotic portal hypertension (Table 57.3) is highly suggestive for IPH. Direct portal or hepatic venography is helpful for the diagnosis of IPH because it can demonstrate a narrowing or disappearance of portal vein branches (Fig. 57.2) or a "weeping willow" appearance of the hepatic vein branches with direct communication between hepatic veins. The examination of liver histology is recommended if differential diagnosis from liver cirrhosis is not certain.

57.5.3 Treatment

The treatment of gastroesophageal varices is the most important when treating IPH patients. The treatment of active bleeding and prophylaxis of variceal bleeding in IPH patients is the same as those in patients with liver cirrhosis. However, preserved liver function in IPH patients allows more diverse treatment options than liver cirrhosis patients with advanced liver dysfunction. The treatments for ascites, hepatic encephalopathy, or portal vein thrombosis are also the same as those for cirrhotic patients.

Severe thrombocytopenia is another complication of IPH that needs to be treated once blood platelet counts are less than 30,000/mL or a tendency tobleed easily appears. The treatment methods for severe thrombocytopenia are splenectomy under open or laparoscopic surgery or partial splenic artery embolization with interventional radiology technique. A recently developed thrombopoietin receptor agonist may provide a novel pharmacotherapy agent for thrombocytopenia in portal hypertension in the future [28].

57.5.4 Prognosis

The clinical course and overall survival is well maintained in IPH patients whose gastroesophageal varices are effectively controlled [29, 30]. Liver cancer rarely develops in the IPH liver, which is quite different from liver cirrhosis. However, complications such as refractory ascites or ectopic varices in the intestine may

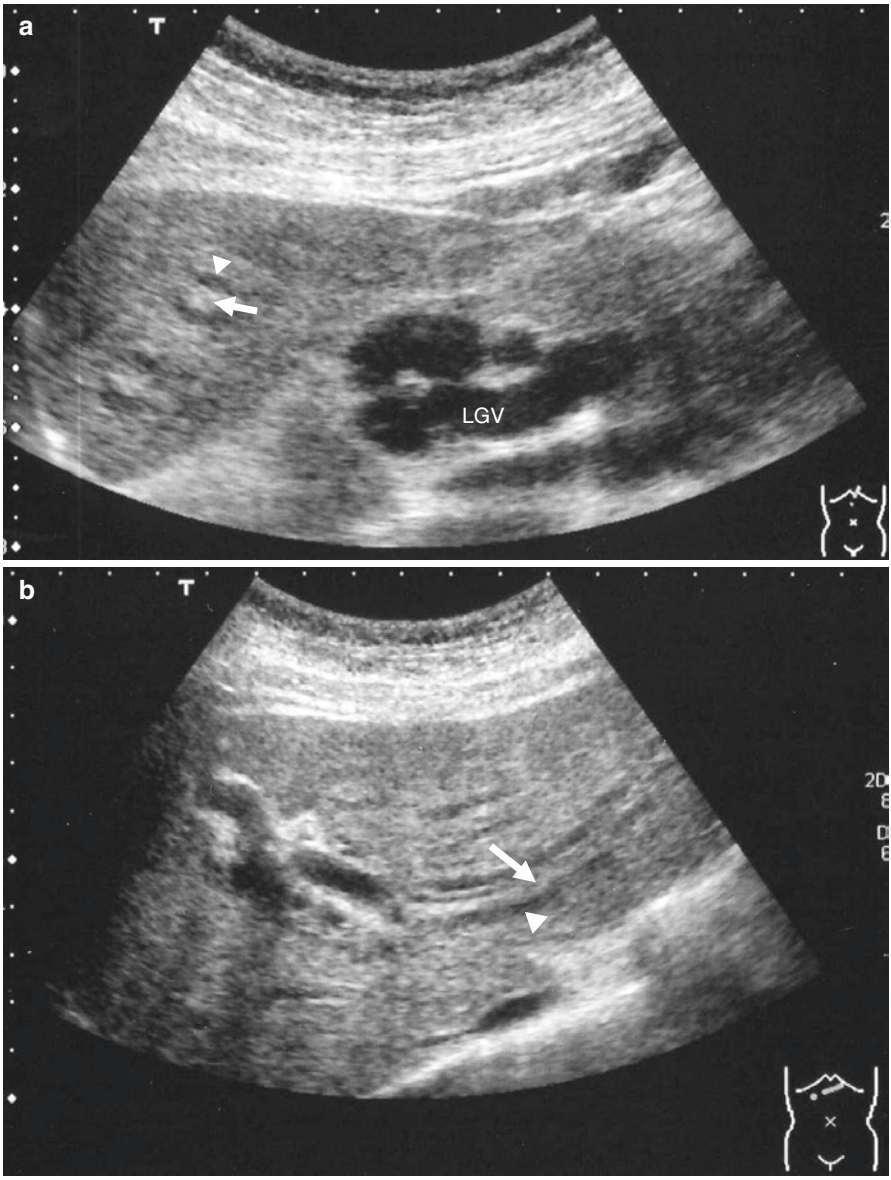


Fig. 57.3 Sonographic images of the liver with IPH. (**a**) Longitudinal image of the left lobe. (**b**) Transverse image of the left lobe. Hypoechoic rim (arrow head) around hyperechoic wall of the portal vein branch (arrow) is frequently observed in the liver with IPH (left gastric vein, LGV)

Table 57.3 Causes of non-cirrhotic portal hypertension for the differential diagnosis of IPH

• Extrahepatic portal vein obstruction • Portal vein thrombosis
• Arterioportal fistula
• Drugs and chemicals
Methotrexate Azathioprine Oxaliplatin
Amiodarone Didanosine Vinyl chloride
• Congenital hepatic fibrosis
• Schistosomiasis • Sarcoidosis • Amyloidosis
• Myeloproliferative disorders • Malignant lymphoma
• Primary biliary cholangitis • Sclerosing cholangitis
• Hepatic venous outflow obstruction • Right heart failure

appear in the late stages of the disease or in patients with advanced portal vein thrombosis [31]. The main causes of death due to IPH have changed over the years because of improved management of gastroesophageal varices, which were previously a major cause of death. The major causes of death in recent years have been infectious diseases, chronic portal hypertension-related organ failure, and aging-related disorders.

References

1. Okuda K. Noncirrhotic portal hypertension. In: Okuda K, Mitchell DG, Itai Y, Ariyama J, editors. Hepatobiliary diseases pathophysiology and imaging. London: Blackwell Science; 2001. p. 287–314.
2. Banti G. Del l'anemia splenica. Arch di Scuola d'Anat Patol (Firenze). 1983;2:53–122.
3. Banti G. Ueber Morbus Banti Folia Haematol. 1910;10:33–74.
4. Hsia DYY, Gellis SS. Portal hypertension in infants and children. Am J Dig Child. 1955;90:290–8.
5. Polish E, Christie J, Cohen A, et al. Idiopathic portal hypertension (Banti's syndrome). Ann Intern Med. 1962;56:624–7.
6. Williams P, Parsonson A, Somers K. Portal hypertension in idiopathic tropical splenomegaly. Lancet I. 1966;287:329–33.
7. Ramalingaswarmi B, Wig HL, Sarma SK. Cirrhosis of the liver in northern India: pathological study. Arch Intern Med. 1962;110:350–8.
8. Mikkelsen WP, Edmondson HA, Peters RL, et al. Extra- and intra-hepatic portal hypertension without cirrhosis (hepatoportal sclerosis). Ann Surg. 1965;162:602–20.
9. Boyer JL, Sengupta KP, Biswas SK, et al. Idiopathic portal hypertension: comparison with portal hypertension of cirrhosis and extrahepatic portal vein obstruction. Ann Intern Med. 1967;66:41–68.
10. Schouten JNL, Garcia-Pagan JC, Valla DC, Janssen HLA. Idiopathic noncirrhotic portal hypertension. Hepatology. 2011;54:1071–81.
11. Kotani K, Kawabe J, Morikawa H, et al. Comprehensive screening of gene function and networks by DNA microarray analysis in Japanese patients with idiopathic portal hypertension. Mediat Inflamm. 2015;2015:349215. https://doi.org/10.1155/2015/349215. Epub 2015 Oct 4.

12. Tsuneyama K, Harada K, Katayanagi K, et al. Overlap of idiopathic portal hypertension and scleroderma: report of two autopsy cases and a reviewer of literature. J Gastroenterol Hepatol. 2002;17:217–23.
13. Okabayashi A. Experimental production of noncirrhotic portal hypertension and splenomegaly with prolonged antigenic stimulation. In: Okuda K, Omata M, editors. Idiopathic portal hypertension. Tokyo: University of Tokyo press; 1983. p. 197–217.
14. Kono K, Ohnishi K, Omata M, et al. Experimental portal fibrosis produced by intraportal injection of killed nonpathogenic E. coli in rabbits. Gastroenterology. 1988;94:787–96.
15. Akahoshi T, Hashizume M, Tanoue K, et al. Role of the spleen in liver fibrosis in rat may be mediated by growth factor beta-1. J Gastroenterol Hepatol. 2002;17:59–65.
16. Sato Y, Nakanuma Y. Role of endothelial-mesenchymal transition in idiopathic portal hypertension. Histol Histopathol. 2013;28:145–54.
17. Morikawa H, Tamori A, Nishiguchi S, et al. Expression of connective tissue growth factor in the human liver with idiopathic portal hypertension. Mol Med. 2007;13:240–5.
18. Hirota Y, Annual Report of Research Committee on Portal Hemodynamics Abnormalities, The Ministry of Health Labor and Welfare of Japan;2006:82–92 (Japanese).
19. Okudaira M, Ohbu M, Okuda K. Idiopathic portal hypertension and its pathology. Semin Liver Dis. 2002;22:59–71.
20. Futagawa S, Fukazawa M, Horisawa M, et al. Portographic liver changes in idiopathic noncirrhotic portal hypertension. AJR. 1980;134:917–23.
21. Okuda K, Kono K, Ohnishi K, et al. Clinical study of eighty-six cases of idiopathic portal hypertension and comparison with cirrhosis with splenomegaly. Gastroenterology. 1984;86:600–10.
22. Futagawa S, Fukazawa M, Musha H, et al. Hepatic venography in noncirrhotic idiopathic portal hypertension. Radiology. 1981;141:303–8.
23. Hillaire S, Bonte E, Denninger MH, et al. Idiopathic non-cirrhotic intrahepatic portal hypertension in the West: a re-evaluation in 28 patients. Gut. 2002;51:275–80.
24. Matsutani S, Maruyama H, Akiike T, et al. Study of portal vein thrombosis in patients with idiopathic portal hypertension in Japan. Liver Int. 2005;25:978–83.
25. Matsutani S. Blood coagulation inhibitors and portal vein thrombosis in patients with portal hypertension. Annual Report of Research Committee on Portal Hemodynamics Abnormalities, The Ministry of Health Labor and Welfare of Japan;2009:31–5 (Japanese).
26. Ohnishi K, Saito M, Sato S, et al. Portal hemodynamics in idiopathic portal hypertension (Banti's syndrome) comparison with chronic persistent hepatitis and normal subjects. Gastroenterology. 1987;92:751–8.
27. Furuichi Y, Moriyasu F, Taira J, et al. Noninvasive diagnostic method for idiopathic portal hypertension based on measurements of liver and spleen stiffness by ARFI elastography. J Gastroenterol. 2013;48:1061–8.
28. Qureshi K, Patel S, Meillier A. The use of thrombopoietin receptor agonist for correction of thrombocytopenia prior to elective procedures in chronic liver diseases: review of current evidence. Int J Hepatol. 2016;2016:1802932. Epub 2016 Oct 9.
29. Ichimura S, Sasaki R, Takemura Y, et al. The prognosis of idiopathic portal hypertension in Japan. Intern Med. 1993;32:441–4.
30. Murai Y, Ohfuji S, Fukushima W, et al. Prognostic factors in patients with idiopathic portal hypertension: two Japanese nationwide epidemiological surveys in 1999 and 2005. Hepatol Res. 2012;42:1211–20.
31. Sawada S, Sato Y, Aoyama H, et al. Pathological study of idiopathic portal hypertension with an emphasis on cause of death based on records of annuals of pathological autopsy cases in Japan. J Gastroenterol Hepatol. 2006;22:204–9.

Chapter 58
Budd-Chiari Syndrome

Yukio Kuniyoshi

Abstract We operated on 69 patients with Budd-Chiari syndrome (BCS) using an operative procedure we devised, 59 of whom were enrolled in this study. From their data, the characteristics of BCS in our surgical patient group were evaluated. The inferior vena cava (IVC) was occluded completely in 43 patients and severely stenotic in 16 patients. The number of patent hepatic veins (HVs) ranged from 0 to 3 per patient, and an average of 1.2 ± 0.72. Esophageal varices (EVs) were found in 52 patients (88.1%). Histologic classification of the specimen obtained in the surgery was liver cirrhosis in 35 patients, liver fibrosis in 18 patients, and liver congestion in 6 patients. Fibrous tissue in liver parenchyma increased with aging. A good correlation existed between liver histology and patient age. Hepatocellular carcinoma (HCC) was found in 12 patients (20.3%) diagnosed before or after BCS surgery and was basically treated by surgical excision. After BCS surgery, EVs disappeared in 14 patients in the early postoperative period and in 5 patients in the late postoperative period. The mean number of patent HVs increased from 1.2 ± 0.72 per patient to 2.41 ± 0.80 per patient. The pressure gradient between infraoccluded IVC and right atrium decreased from 12.9 ± 3.72 to 4.67 ± 2.97 mmHg.
In summary, occlusion of HVs irrespective of IVC occlusion induces liver congestion, resulting in increasing fibrous tissue in liver parenchyma and increasing portal pressure. By reopening the occluded HVs surgically, the EVs disappear, and the increase of fibrous tissue can be inhibited.

Keywords Budd-Chiari syndrome · Hepatic outflow occlusion · Portal hypertension · Esophageal varices

Y. Kuniyoshi (✉)
Department of Thoracic and Cardiovascular Surgery, Graduate School of Medicine, University of the Ryukyus, Nishihara-cho, Okinawa, Japan
e-mail: kuni9244@med.u-ryukyu.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_58

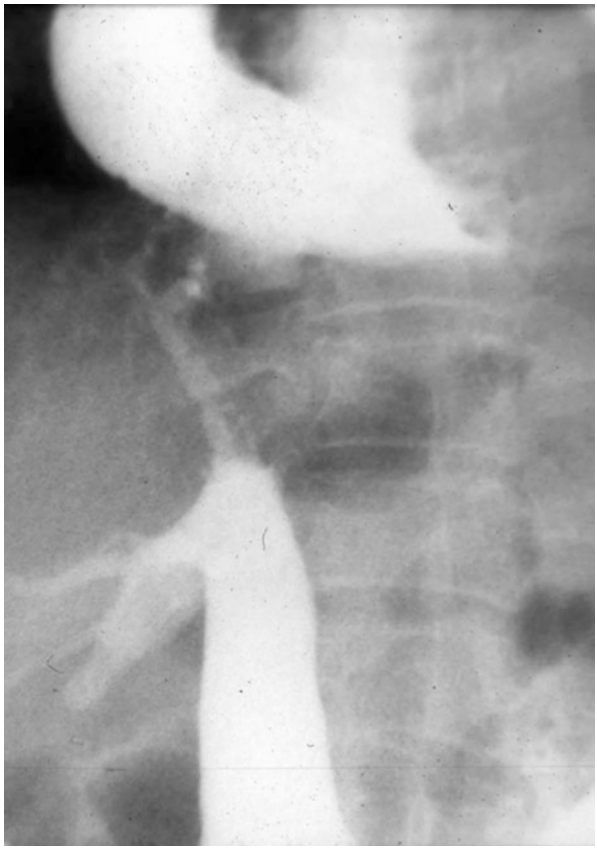


Fig. 58.1 Venogram of the inferior vena cava (IVC). In patients with BCS, a bidirectional venogram from the infraoccluded IVC and the right atrium elucidates the site of IVC occlusion. A long segment of retrohepatic IVC, middle hepatic vein, and left hepatic veins are occluded

58.1 Introduction

Budd-Chiari syndrome (BCS) has been defined as a disorder caused by hepatic venous outflow occlusion at any level from the hepatic venules, the main three hepatic veins, and the inferior vena cava (IVC) to the right atrium (Fig. 58.1). Historically, the British physician George Budd in 1845 and the Austrian pathologist Hans Chiari in 1899 each reported cases of hepatic vein obstruction [1, 2], leading to the naming of Budd-Chiari syndrome. The natural history of BCS is not well known, because no cohorts of untreated patients have been reported. Therapeutic options for BCS include medical management with anticoagulation therapy, decompressing therapies such as recanalization strategies (thrombolytic therapy, stenting, and angioplasty), surgical shunting and transjugular intrahepatic portosystemic shunt (TIPS) [3], and orthotopic liver transplantation (OLT) [4, 5]. We have operated on 69 patients in the last 37 years using an operative procedure we devised that allows a direct approach to and repair of the occlusive sites [6–8]. From these surgical cases, we describe (1) the history of surgical repair in Japan for BCS, (2) progression of BCS, (3) esophageal varices (EVs) as a complication of BCS, and (5) the relationship between EVs and the histology of the liver.

58.2 History

Some etiological differences in BCS exist between the East and the West. In the West, BCS is based on hypercoagulopathy, and anticoagulant therapy is recommended as the first line of treatment. The flow map of the strategy for BCS treatment shows that OLT is recommended [4, 5]. In Japan, few reports have described liver transplantation for the treatment of BCS. Historically, a direct surgical approach has been developed in Japan. Kimura reported cases of BCS treated by trans-right atrial membranotomy with successful results [9]. Manabe directly approached the affected lesion through a right thoracoabdominal incision and performed excisional treatment of the obstacle in the IVC [10]. Koja et al. introduced cardiopulmonary bypass (CPB) as support for caval clamping to stem massive bleeding from the IVC incision site. The introduction of CPB creates sufficient time to achieve IVC and hepatic vein (HV) repair [6].

58.3 Patients

58.3.1 Underlying Diseases

We have operated on 69 patients with BCS using the operative procedure we devised at Ryukyu University Hospital over the last three decades. Preoperatively, major symptoms or signs of lower extremity edema were seen in 11 patients, abdominal distension in 11, hepatic encephalopathy in 6, hepatomegaly in 5, superficial collateral veins on the abdomen in 5, varicose veins or pigmentation of the legs in 5, gastrointestinal bleeding in 5, and abdominal pain in 2. Underlying disorders comprised Behçet's disease in three, protein C deficiency in six, protein S deficiency in five, and antiphospholipid antibody syndrome in one. Postoperatively, two patients died during hospitalization. The remaining patients were discharged in a good state. Of these 67 patients, we enrolled the 59 patients with complete data for evaluation in this study. Twenty-two patients were female. Patient age at surgery ranged from 21 to 73.3 years, with a mean of 46.3 ± 13.0 years.

58.3.2 Pattern of IVC Occlusion and Patency of HVs

The IVC was occluded completely in 43 patients, and severely stenotic in 16 patients. According to intraoperative findings, the length of the occluded IVC ranged from 0.5 to 15.0 cm, with an average of 3.58 ± 2.82 cm. The average number of patent HVs was 1.22 ± 0.74 per patient. Forty-seven patients (79.7%) had a patent right HV (Table 58.1). The pressure gradient between the infra-IVC occlusion site and right atrium was 12.9 ± 3.72 mmHg (range, 4.0–21.0 mmHg).

Table 58.1 Number and distribution of patent HVs

	Location of patent HVs	Number
All occlusion	–	8
A single patent HV	Left HV	2
	Middle HV	2
	Right HV	32
Double patent HVs	Right and left HVs	6
	Right and middle HVs	5
All patent HVs	–	4
Total		59

The average number of patent HVs was 1.22 ± 0.74 per patient. The highest patency rate of HVs was 47/59 (79.7%), for right HVs.

Table 58.2 Relationship between EVs and liver histology

Histological classification	No. of patients	Female	Age (Avg. ± SD)	EV (positive) (%)[a]	RC (positive) (%)[b]
Liver congestion	6	3	31.0 ± 7.04	4 (66.7%)	0 (0%)
Liver fibrosis	18	6	42.7 ± 12.9	15 (83.3%)	7 (46.7%)
Liver cirrhosis	35	13	50.9 ± 11.2	33 (94.3%)	8 (24.2%)

Among the three groups, age differed significantly ($P < 0.036$). Older patients were considered to have more fibrous liver parenchyma. If age correlates with duration of illness with BCS, fibrosis of the liver might proceed with duration of liver congestion.

[a](%) percentage of the number of the patients EVs positive in each group

[b](%): percentage of the number of the patients RC sign positive in each group

58.3.3 EVs

EVs are formed by increasing portal vein pressure and emerge with over 12 mmHg of portal vein pressure. Preoperatively, EVs were found in 52 patients (52/59; 88.1%), 15 of whom showed a positive red color (RC) sign, as a warning sign for variceal vein rupture. EVs in BCS directly reflect portal vein pressure, and portal vein pressure in BCS is increased not only by liver vein congestion but also liver parenchymal fibrosis progressed by sustained hepatic venous occlusion.

58.3.4 Relationship Between EVs and Liver Histology

Occlusion of hepatic venous outflow induces liver vein congestion, which leads to tissue ischemia, followed by hepatocyte necrosis. With the regeneration of liver parenchyma after hepatocyte necrosis, fibrous tissue increases, elevating intrahepatic blood flow resistance and subsequently portal vein pressure. During surgery, liver specimens were obtained for microscopic evaluation. EVs in BCS are formed by high portal vein pressure induced by increasing intrahepatic flow resistance in the portal vein. The high resistance of portal vein consists of two factors: occlusion

of HVs and fibrous tissue of liver parenchyma. Liver specimens were microscopically classified into three groups: liver congestion, liver fibrosis, and liver cirrhosis. Table 58.2 shows the relationship between EVs and histological classification of the liver. A significant difference in age was evident among the three groups. With aging of the patients, fibrous tissue in the liver tends to increase, and the combined rate of patients with EVs also. Progression through each stage in the histological classification takes about 10 years.

58.4 Surgical Treatment

58.4.1 Our Operative Method

In general, the surgical treatment consists of two types of approach: indirect approach and the direct approach including our operative procedure. The occluded sites of the IVC and the HVs are directly dissected and are reopened under a cardiopulmonary bypass (CPB). CPB is essential to our method. The patient is positioned in a left hemilateral decubitus position. The target IVC located behind the liver is exposed by thoracotomy and subsequent upper partial laparotomy, followed by circumferential incision of the diaphragm. Under CPB, the lesional site of the IVC is repaired under direct visualization. Massive bleeding from patent HVs is sucked into the CPB circuit and returned to the body. An occluded or severely stenotic IVC is recanalized by excision of the obstacle and repaired by patch plasty with autopericardium. The schema of Fig. 58.2 shows the concept of our surgical procedure.

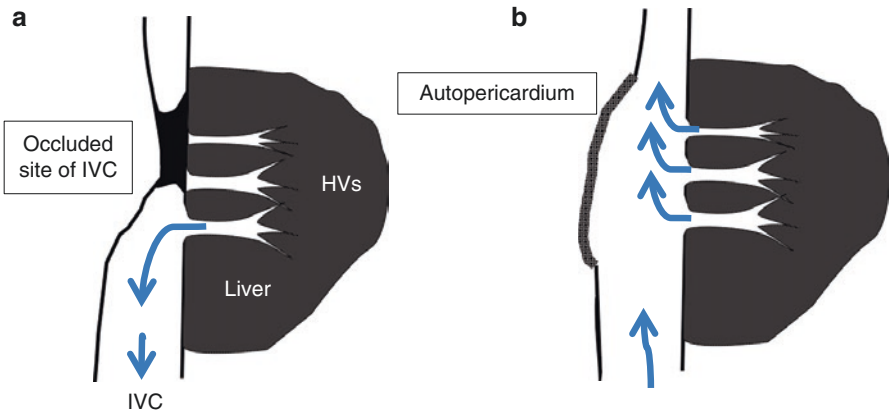
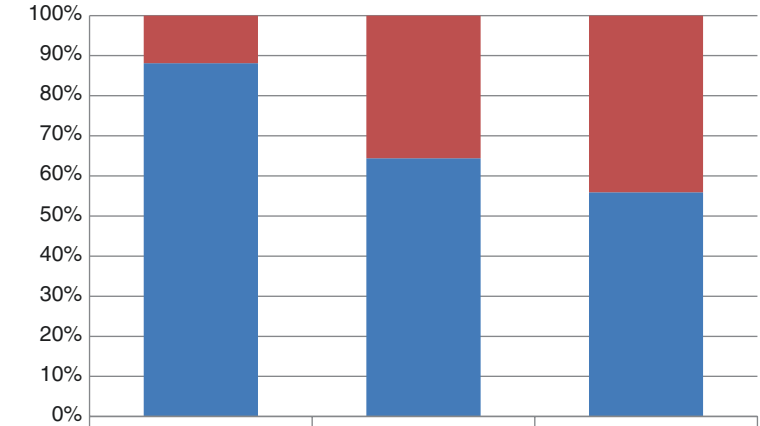


Fig. 58.2 (**a**) Preoperative schema: Inferior vena cava (IVC) occlusion leads to occlusion of two hepatic veins (HVs). One of the HVs, usually the right HV, is patent. (**b**) Post-reconstruction schema: Excision of the obstacle opens the occluded ostia of two HVs. The incised IVC is dilated with harvested autopericardium

58.4.2 Results

Postoperatively, the mean number of patent HVs increased from 1.4 ± 0.7 to 2.5 ± 0.7. Pressure in the infrahepatic IVC decreased from 17.8 ± 4.4 to 8.7 ± 3.4 mmHg, and the pressure gradient between the infrahepatic IVC and right atrium decreased from 12.9 to 4.8 ± 3.0 mmHg. The indocyanine green clearance test at 15 min decreased from 30.7 ± 17.2 to 21.6 ± 14.9%. EVs disappeared in the early postoperative period at discharge in 14 patients, comprising 3 patients with liver congestion, 5 patients with liver fibrosis, and 6 patients with liver cirrhosis. Patients were followed up for a period from 0.2 to 28.1 years, with an average of 10.5 ± 6.9 years. During follow-up, EVs disappeared in five patients in the late postoperative period. Eighteen late deaths were caused by hepatocellular carcinoma (HCC) in seven patients, Behcet's disease in two patients, pancreatic carcinoma in one, pneumonia in one, liver failure in one, suicide in one, others in one, and unknown cause in four. Discharged patients were followed up on an outpatient basis at least twice a year and were evaluated by endoscopy and enhanced CT for patency of the reconstructed IVC and HVs. Patients who did not visit an outpatient clinic for 5 years were considered "dropout patients." Twenty-one patients were lost to outpatient follow-up, and the follow-up rate at the end of 2014 was 68.7% (Fig. 58.3).



	Preope.	Postope. at discharge	Late postope. date
EV(-)	7.0	21.0	26.0
EV(+)	52.0	38.0	33.0

Fig. 58.3 Pre- and postoperative course of esophageal varices. EVs had disappeared in 14 patients in the early postoperative period at discharge and in 5 patients in the late postoperative period

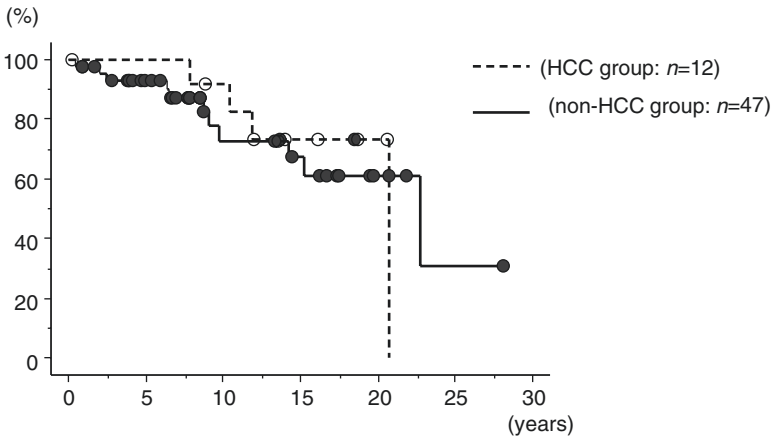


Fig. 58.4 Postoperative cumulative survival curve. Study patients were divided into two groups: a HCC group and a non-HCC group. No significant difference is apparent between the two groups (log-rank, $P = 0.88$)

58.4.3 Hepatocellular Carcinoma (HCC)

HCC was associated with BCS in 12 patients (17.4%) who were diagnosed pre- or postoperatively. All patients were treated by surgical resection after or concomitantly with BCS surgery. HCC was initially treated with transarterial chemoembolization (TACE) and was resected surgically 2 or 3 weeks later. The underlying liver histology was liver cirrhosis in eight patients and liver fibrosis in four patients. No HCC was seen in patients with liver congestion. No significant difference in cumulative survival rate was seen between HCC and non-HCC groups (Fig. 58.4). HCC was therefore not a risk factor for survival rate after surgery in our study group.

58.5 Case Presentations

58.5.1 The Patient Was a 30-Year-Old Woman

She suffered abdominal distension from 2 months after delivery and was diagnosed with BCS after abdominal echogram, CT, and MRI showing IVC stenosis and severe stenosis of the right and left hepatic veins at the ostia. The patient consulted our department and underwent our operative procedure. The stenotic ostia of both hepatic veins were resected, comprising mainly endothelium of thickened IVC and some liver parenchyma to reach the normal HVs. The stenotic IVC was repaired by resecting thickened IVC and dilated with autopericardium. A postoperative pressure

study showed decrease from 22 to 10 mmHg and normalization of hepatic venous wedge pressure from 22 to 7 mmHg. Microscopic diagnosis of the harvested specimen was liver congestion. EVs found preoperatively disappeared by 4 weeks after surgery. The patient has been well as of 9 years after surgery.

58.5.2 The Patient Was a 48-Year-Old Man

Preoperatively, the patient had an occluded IVC and patent right hepatic vein. He underwent our operative procedure and had been well. The occluded IVC and occluded hepatic veins were both patent. Microscopic diagnosis of the liver specimen showed liver cirrhosis (LC). The pressure gradient between the infraoccluded IVC and right atrium was 11 mmHg preoperatively and decreased to 4.5 mmHg. At discharge, EVs remained evident, and the patient was followed up on an outpatient basis yearly with endoscopic evaluation of the esophagus and stomach, enhanced CT, and determination of serum AFP (alpha-fetoprotein). EVs disappeared 4 years after surgery. He was diagnosed with HCC 8 years and 2 months after BCS surgery and underwent HCC resection surgery after TACE. The liver specimen harvested during surgery for HCC was compared with the specimen at BCS surgery. Blood congestion in intrahepatic vessels was alleviated, although basic volume of intercellular fibrous tissue remained.

58.5.3 The Patient Was a 40-Year-Old Man

He underwent our surgery and has been well after surgery. The occluded IVC and associated occluded left hepatic veins were reopened. A RC sign in preoperative EVs disappeared on early postoperative endoscopic evaluation. During the follow-up period, endoscopic evaluation showed a positive RC sign 6 years after surgery. Reevaluation of IVC and HVs by echogram showed occlusion of both vessels. Reoperation was carried out utilizing expanded polytetrafluoroethylene (e-PTFE) graft for patch dilation as a substitute of autopericardium. After surgery, the RC sign had disappeared.

58.6 Conclusions

1. In BCS, the hepatic outflow tract is occluded, inducing liver congestion. If liver congestion continues, liver parenchyma might start to become fibrotic, resulting in liver cirrhosis.
2. Portal hypertension is established in the early stage after hepatic outflow tract occlusion. Four patients (66.7%) among the six patients who had liver conges-

tion on microscopic examination had EV preoperatively. Fibrosis of the liver parenchyma might progress during persistence of liver congestion. After surgical reopening of the occluded HVs, EVs remain because of liver fibrosis. Earlier interventional treatment should be carried out to protect against progression of liver deterioration.

3. HCC associated with BCS might originate with liver congestion. Patients with BCS should be scrutinized for HCC and followed carefully throughout life.

References

1. Budd G. On Diseases of the Liver. !st Ed. London: John Churchil; 1845.146
2. Chiari H. Ueber die silbstandinge phlebitis obliterans der hauptstamme der venae hepaticae als todesursache. Beitr Pathol Anat. 1899;26:1–18.
3. Horton JD, San Miguel FL, Membreno F, Wright F, Paima J, Foster P, Ortiz JA. Budd-Chiari syndrome: illustrated review of current management. Liver Int. 2008;28:455–66.
4. Martens P, Nevens F. Budd-Chiari syndrome. Gastroenterol J. 2015;3:489–500.
5. Zeitoun G, Escolano S, Hadengue A, Azar N, El Younsi M, Mallet A, Boudet MJ, Hay JM, Erlinger S, Benhamou JP, Belghiti J, Valla D. Outcome of Budd-Chiari syndrome: a multivariate analysis of factors related to survival including surgical portosystemic shunting. Hepatology. 1999;30:84–9.
6. Koja K, Kusaba A, Kuniyoshi Y, Iha K, Akasaki M, Miyagi K. Radical open endvenectomy with autologous pericardial patch graft for correction of Budd-Chiari syndrome. Cardiovasc Surg. 1996;4:500–4.
7. Kuniyoshi Y, Koja K, Akasaki M, Miyagi K, Shimoji M, Kudaka M, Uezu T. Improvement in esophageal varices and liver histology postoperatively in Budd-Chiari syndrome. Ann Thorac Surg. 1998;65:1711–4.
8. Inafuku H, Morishima Y, Nagano T, Arakaki K, Yamashiro S, Kuniyoshi Y. A three-decade experience of radical open endvenectomy with pericardial patch graft for correction of Budd-Chiari syndrome. J Vasc Surg. 2009;50:590–3.
9. Kimura C. Surgical treatment of portal hypertension of post-hepatic origin, with special reference to trans-cardiac membranotomy for membranous obstruction of the hepatic portion of the inferior vena cava. Jpn Circ J. 1964;28:181–3.
10. Manabe H. Endovenectomy for the surgical treatment of Budd-Chiari syndrome. Jpn Circ J. 1964;28:183–6.

Chapter 59
Extrahepatic Portal Vein Obstruction

Shoichi Matsutani and Hideaki Mizumoto

Abstract Extrahepatic portal vein obstruction (EHO) is a disease presenting portal hypertension caused by the obliteration of the prehepatic portion of the portal vein, including the branches at the hepatic hilum. Secondary portal vein thrombosis with diverse background diseases is considered to make an occlusion of the portal vein which leads to the development of EHO. The basic pathophysiology of EHO includes portal hypertension due to prehepatic block of portal blood flow and well-preserved liver function without development of cirrhotic changes of the liver. Furthermore, cavernomatous transformation of the portal vein (CTPV), which is a consequence of the development of hepatopetal collateral vessels around the obliterated portal vein, is directly associated with the pathophysiology of EHO and contributes to the image diagnosis of the disease. Chronic or refractory ascites is uncommon compared with patients with liver cirrhosis. Some patients show biliary symptoms due to CTPV around the bile duct which is called portal biliopathy. Indications and methods for the treatment of gastroesophageal varices and hypersplenism are the same as those for portal hypertension with other causes. For symptomatic portal biliopathy, endoscopic or intervention radiology management is employed. For complete reduction of elevated portal pressure, trials of stent placement over the obstructed portal vein with intervention radiology have been reported, although clinical experience is limited. The overall prognosis is usually good except in patients with severe portal biliopathy or uncontrollable gastrointestinal varices.

Keywords Extrahepatic portal obstruction · Cavernomatous transformation of the portal vein · Portal cavernoma · Portal biliopathy

S. Matsutani (✉) · H. Mizumoto
Department of Gastroenterology, Funabashi Municipal Medical Center, Funabashi, Chiba, Japan
e-mail: matsu803@pg7.so-net.ne.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_59

59.1 Introduction

Extrahepatic portal vein obstruction (EHO) is a disease presenting portal hypertension caused by the obliteration of the prehepatic portion of the portal vein, including the branches at the hepatic hilum [1]. The obstruction sometimes extends to the splenic vein, superior mesenteric vein, or intrahepatic portal vein branches. The disease was first recognized in the late nineteenth century following a postmortem study [2]. Since then, further pathomorphological studies have clarified the presence of a cavernomatous transformation of the portal vein (CTPV) observed in and around the obliterated portal vein [3]. This unique feature of the obliterated portal vein, which is a consequence of the development of hepatopetal collateral vessels, is directly associated with the pathophysiology of EHO and contributes to the diagnosis of the disease. In this chapter, clinical aspects of Japanese patients with noncirrhotic EHO, which develops without preexisting liver cirrhosis or portal hypertension of other causes, are presented and discussed [4, 5].

59.2 Pathophysiological Aspects

59.2.1 Etiology

Background diseases, other than liver cirrhosis, that cause EHO include inherited or acquired hypercoagulable diseases (prothrombin gene mutation; deficiency of protein C, protein S, and antithrombin III; and chronic myeloproliferative disease), infectious diseases (sepsis, including neonatal or umbilical sepsis, pylephlebitis, severe enterocolitis, advanced appendicitis, subacute bacterial endocarditis, and postoperative infection), and local injuries to the portal vein system (biliary tract disease, pancreatitis, tumors, duodenal ulcer, trauma, abdominal interventional radiology (IVR), and surgery) [6–8]. Secondary portal vein thrombosis with these background diseases is considered to make an occlusion of the portal vein which leads to the development of EHO. Some congenital or developmental abnormalities, such as an agenesis of the portal vein, have been speculated to be associated with EHO because of the high frequency of the disease in childhood portal hypertension, although this remains controversial [9–11]. However, the exact causes of primary or idiopathic EHO remain unclear despite knowledge of clinical history or laboratory examination of patients.

59.2.2 Epidemiology

The incidence of EHO is lower than idiopathic portal hypertension (IPH), and the number of patients with EHO is rapidly decreasing in Japan, according to a national survey conducted by the Japanese Research Committee for the Study of Portal Hemodynamic Abnormalities (1998, 720 patients and 2004, 450 patients) [12]. The age distribution of patients with EHO has two peaks: one before the age of 20 and

the other between 40 and 60 years of age. In Japan, the disease is predominant in males; the male to female ratio is 1:0.6, which is quite different compared with that in patients with IPH.

59.2.3 Pathophysiology

The basic pathophysiology of EHO includes portal hypertension due to prehepatic block of portal blood flow and well-preserved liver function without development of cirrhotic changes of the liver. In contrast to IPH, liver histology shows minimal changes from almost normal architecture to minimal fibrotic changes which are associated with well-preserved liver function throughout the course of EHO. Also specific to EHO is the formation of collateral circulation around the obliterated portal vein, known as CTPV or portal cavernoma (Figs. 59.1 and 59.2). The form

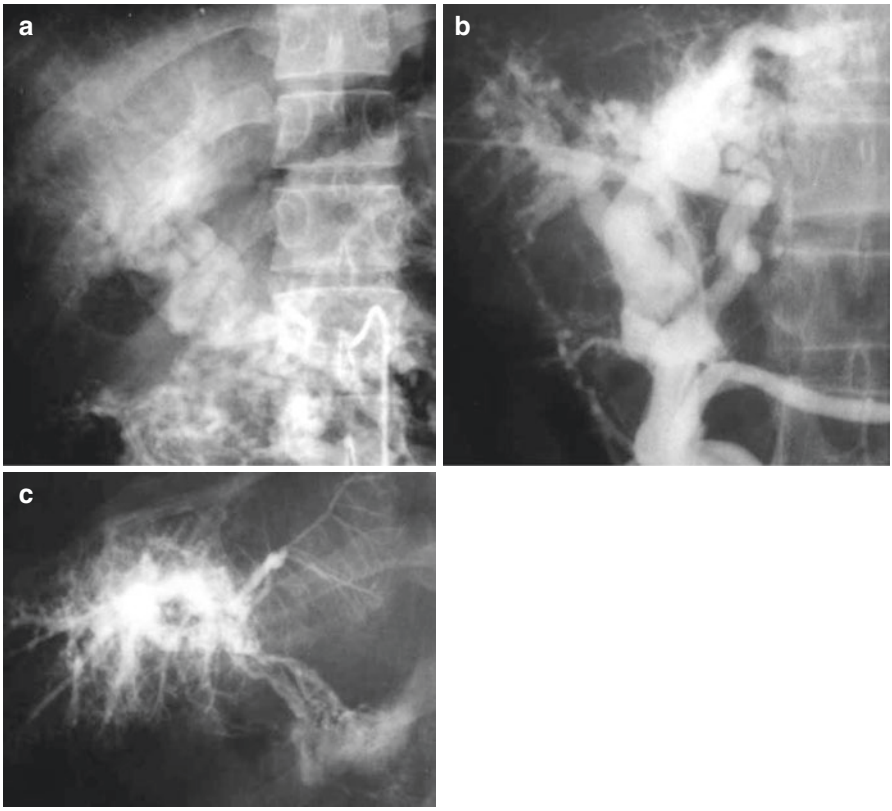


Fig. 59.1 Angiographic images of EHO. (**a**) CTPV showing fine vessels with tortuous running. (**b**) CTPV showing bar-like vessels with straight running. (**c**) Intrahepatic portal vein showing irregular and narrow branches

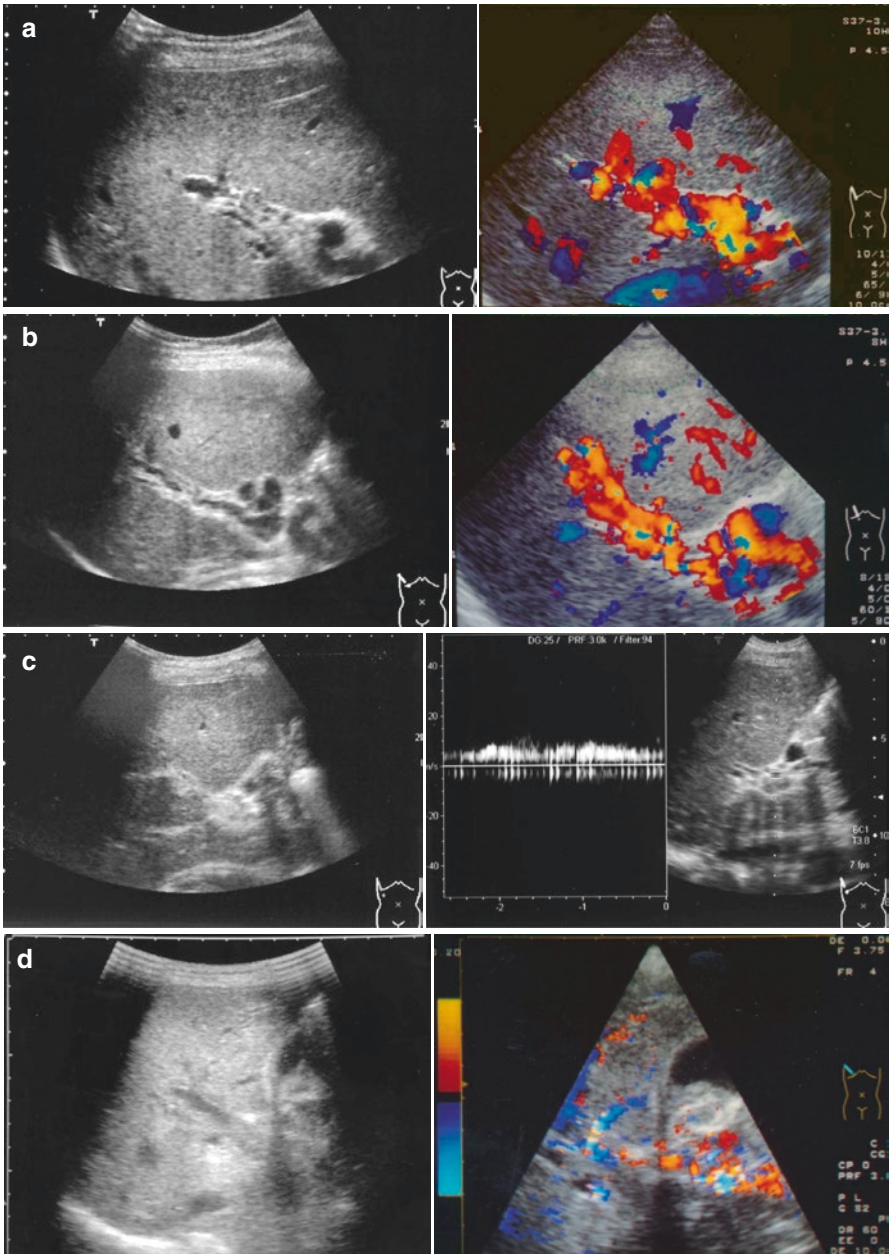


Fig. 59.2 Sonographic images of EHO (left, gray scale; right, Doppler). (**a**) CTPV showing spongelike appearances with well-developed collaterals. (**b**) CTPV showing spongelike appearances with fine collaterals. (**c**) CTPV showing poor development of spongelike collaterals. (**d**) CTPV developed around portal vein thrombosis in a patient with pancreatitis. (**e**) CTPV developed in the wall of gall bladder

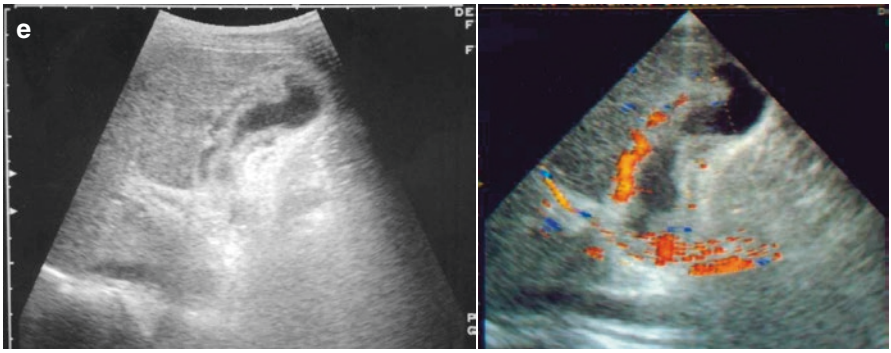


Fig. 59.2 (continued)

and location of CTPV are different in each patient according to the site and the grade of the development of hepatopetal collateral circulation around the obliterated veins [13]. Well-developed CTPV can occasionally prevent the development of portal hypertension [14]. Although CTPV is important to maintain portal blood flow to the liver, it sometimes causes the specific pathological features of EHO such as compression of the bile duct which leads to bile flow disturbance or bile duct varices (portal biliopathy) [15–17] (Fig. 59.3). Furthermore, acute dilatation of the bile duct with portal biliopathy can influence blood flow in CTPV by compression which can subsequently worsen portal hypertension (personal experience). Another problem associated with CTPV is duodenal varices which can develop when the duodenal veins are involved (Fig. 59.4). Besides these specific changes in EHO, splenomegaly with pancytopenia and portal systemic collaterals, including gastroesophageal varices, develop the same way as in portal hypertension of other causes. However, the formation of portal systemic collaterals through the paraumbilical vein is rare, and chronic ascites is uncommon in patients with EHO in whom the circulation in and around the hepatic sinusoid is well preserved [6, 13].

59.3 Clinical Aspects

59.3.1 Clinical Manifestations

Almost half of patients with EHO exhibit hemorrhaging from gastroesophageal varices as an initial symptom, although the development of portal hypertension is insidious in many patients. However, some patients clearly exhibit the onset of portal hypertension after portal vein obliteration, when portal vein thrombosis with background diseases is severely symptomatic. The signs and symptoms of EHO are similar to those of IPH, concerning splenomegaly with decreased peripheral blood cells and gastroesophageal varices with or without hemorrhage. However, chronic or refractory ascites is uncommon in patients with EHO compared with patients

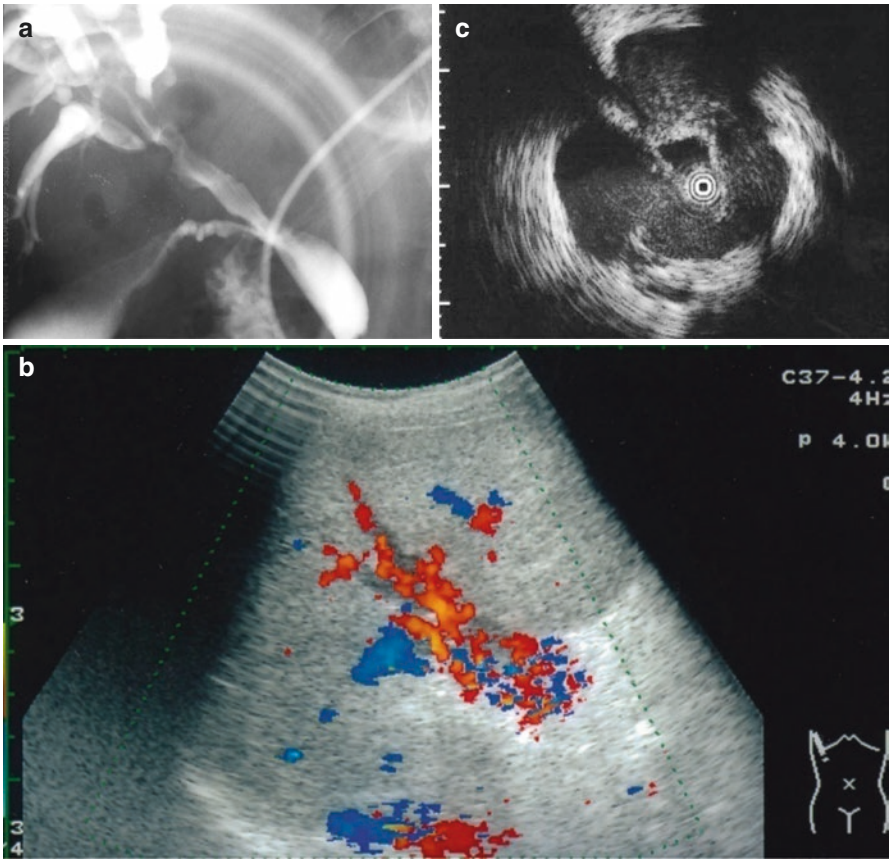


Fig. 59.3 Portal biliopathy in a patient with EHO. (**a**) Cholangiogram. Right intrahepatic bile ducts are dilated with compression of right hepatic duct with CTPV. Patient had recurrent cholangitis due to stricture of the bile duct. (**b**) Color Doppler image. CTPV develops around the bile duct at the hepatic hilum. (**c**) Intraductal ultrasonogram. CTPV is observed just beneath the wall of the bile duct

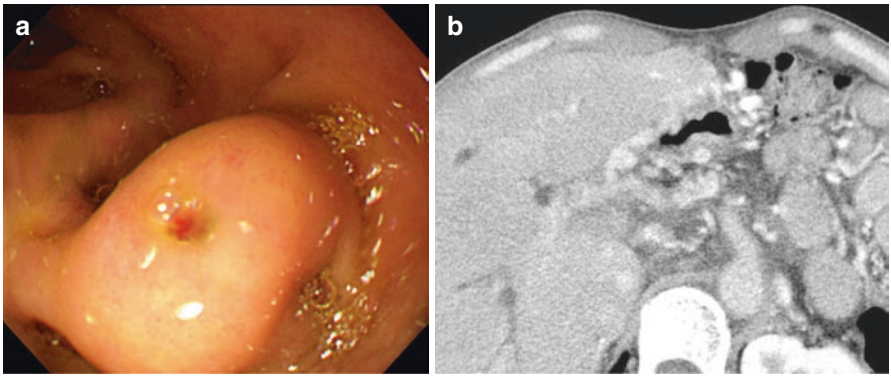


Fig. 59.4 Duodenal varices in a patient with EHO. (**a**) Endoscopic image. Bleeding point is observed at the top of duodenal varices. (**b**) Enhanced computed tomography image. CTPV runs in and around the duodenum.

with liver cirrhosis. Some patients show biliary symptoms like jaundice, biliary colic, or fever when they have advanced portal biliopathy with bile duct stricture, cholelithiasis, or cholangitis, although the majority of patients with portal biliopathy have silent clinical manifestations. Overall, liver function is well preserved during the entire course of the disease.

59.3.2 Diagnosis

Imaging is essential for the diagnosis of EHO [18]. EHO can be identified by the disappearance of normal running lumen in the extrahepatic portal vein system, including porta hepatis and the presence of CTPV. CTPV can be visualized as a mixture of various-sized, tortuous, and winding vessels with complex running, known as a spongelike appearance. However, images vary between patients based on the location or grade of the development of CTPV [19] (Figs. 59.1 and 59.2). Angiography has been employed as the gold standard imaging method for diagnosis. However, recently, ultrasonography with or without Doppler, computed tomography with contrast enhancement, or magnetic resonance imaging have been recommended for a noninvasive diagnosis. Endoscopy is necessary for the management of gastroesophageal varices as it is used in portal hypertension with other causes. Furthermore, observation of the duodenum is important in endoscopic examination because of the risk of duodenal varices in patients with EHO. Magnetic resonance cholangiography and portography are useful for diagnosing portal biliopathy.

59.3.3 Treatment

Indications and methods for the treatment of gastroesophageal varices and hypersplenism are same as those in patients with portal hypertension from other causes. It is important not to reduce the portal blood flow to the liver when treating duodenal or choledochal varices which sometimes develop as a part of CTPV. For symptomatic portal biliopathy (another specific problem associated with EHO), maintenance of bile flow and relief from biliary symptoms are achieved by removing gallstones or dilating a stricture in the bile duct with endoscopic or IVR management [20]. However, portal decompression surgery is recommended for patients in whom the management of portal biliopathy is refractory to noninvasive treatment procedures [21]. For complete reduction of elevated portal pressure, trials of stent placement over the obstructed portal vein with IVR have been reported, although clinical experience is limited [22–24]. In patients with EHO, especially with thrombophilic background diseases, another portal thrombosis should be avoided by monitoring using imaging and an appropriate anticoagulation drug.

59.3.4 Prognosis

According to a national survey in Japan, the overall prognosis is usually good in patients with EHO when gastroesophageal varices are well managed. The cumulative survival rates at 5 and 10 years are 93.3% and 93.3%, respectively [25]. However, difficulties in clinical management remain in cases with ectopic varices or symptomatic portal biliopathy which are refractory to endoscopic or IVR management.

References

1. Moriyasu F, Furuichi Y, Tanaka A, et al. Diagnosis and treatment guidelines for aberrant portal hemodynamics. Hepatol Res. 2017;47:373–86. https://doi.org/10.1111/hepr.12862.
2. Balfour GW, Stewart TG. Case of enlarged spleen complicated with ascites, both depending upon varicose dilatation and thrombosis of the portal vein. Edin Med J. 1868;14:589–98.
3. Klemperer P. Cavernomatous transformation of the portal vein. Arch Pathol. 1928;6:353–77.
4. Okuda K. Non-cirrhotic portal hypertension versus idiopathic portal hypertension. J Gastroenterol Hepatol. 2002;17:S204–13.
5. Kameda H, Yamazaki K, Imai F, et al. Obliterative portal venopathy: a comparative study of 184 cases of extrahepatic portal obstruction and 469 cases of idiopathic portal hypertension. J Gastroenterol Hepatol. 1986;1:139–49.
6. DeLeve LD, Valla DC, Garcia-Tsao G. Vascular disorders of the liver. Hepatology. 2009;49:1729–64.
7. Khanna R, Sarin SK. Non-cirrhotic portal hypertension-diagnosis and management. J Hepatol. 2014;60:421–41.
8. Kimura K, Okuda K, Takara K, et al. Membranous obstruction of the portal vein. A case report. Gastroenterology. 1985;88:571–5.
9. Johnson AO, Obisesan AO, Williams AO. Extrahepatic portal hypertension due to congenital obstruction of the portal vein and associated gross hepatic lobulation. Clin Pediatr. 1979;18:619–21.
10. Odievre M, Pige G, Alagile D. Congenital abnormalities associated with extrahepatic portal hypertension. Arch Dis Child. 1977;52:383–5.
11. Gallego C, Velasco M, Marcuello P, et al. Congenital and acquired anomalies of the portal venous system. Radiographics. 2002;22:141–59.
12. Hirota Y, Annual Report of Research Committee on Portal Hemodynamics Abnormalities, The Ministry of Health Labor and Welfare of Japan;2006:82–92 (Japanese).
13. Gaetano AM, Lafortune M, Patriquin H, et al. Cavernous transformation of the portal vein: patterns of intrahepatic and splanchnic collateral circulation detected with Doppler sonography. AJR. 1995;165:1151–5.
14. Sugiura N, Matsutani S, Ohto M, et al. Extrahepatic portal vein obstruction in adults detected by ultrasound with frequent lack of portal hypertension signs. J Gastroenterol Hepatol. 1993;8:161–7.
15. Sugiura N, Matsutani S, Tsuchiya Y, et al. Biliary tract diseases in extrahepatic portal vein obstruction. Journal of Biliary Tract & Pancreas (KANTANSUI) 1993;14:599–605 (Japanese).
16. Walser EM, Runyan BR, Heckman MG, et al. Extrahepatic portal biliopathy: proposed etiology on the basis of anatomic and clinical features. Radiology. 2011;258:146–53.
17. Le Roy B, Gelli M, Serji B, et al. Portal biliopathy as a complication of extrahepatic portal hypertension: etiology, presentation and management. Visc Surg. 2015;152:161–6.

18. Arora A, Sarin SK. Multimodality imaging of primary extrahepatic portal vein obstruction (EHPVO): what every radiologist should know. Br J Radiol. 2015;88(1052):20150008. https://doi.org/10.1259/bjr.20150008. Epub 2015 May 29.
19. Lafortune M, Patriquin H, Lepanto L. Color Doppler of portal hypertension: a pictorial essay. In: Rossi P, Ricci P, Broglia L, editors. Portal hypertension diagnostic imaging and imaging-guided therapy. Berlin: Springer; 2000. p. 77–91.
20. Saraswat VA, Rai P, Kumar T, et al. Endoscopic management of portal cavernoma cholangiopathy: practice, principles and strategy. J Clin Exp Hepatol. 2014;4(Suppl 1):S67–76.
21. Vibert E, Azoulay D, Aloia T, et al. Therapeutic strategies in symptomatic portal biliopathy. Ann Surg. 2007;246:97–104.
22. Pargewar SS, Desai SN, Rajesh S, et al. Imaging and radiological interventions in extra-hepatic portal vein obstruction. World J Radiol. 2016;8:556–70.
23. Senzolo M, Tibbals J, Cholongitas E, et al. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis with and without cavernous transformation. Aliment Pharmacol Ther. 2006;23:767–75.
24. Wils A, van der Linden E, van Hoek B, Pattynama PM. Transjugular intrahepatic portosystemic shunt in patients with chronic portal vein occlusion and cavernous transformation. J Clin Gastroenterol. 2009;43:982–4.
25. Hashizume M. Annual Report of Research Committee on Portal Hemodynamics Abnormalities, The Ministry of Health Labor and Welfare of Japan;2006:93–6 (Japanese).

Part X
Portal Hypertension and Liver Transplantation

Chapter 60
Portal Hypertension and Liver Transplantation: Current Situation in Japan and Overseas

Junichi Kaneko and Norihiro Kokudo

Abstract Liver transplantation is the only curative treatment option for both portal hypertension and end-stage liver disease (ESLD). In Japan, 50–60 deceased-donor liver transplant (DDLTs) and 400–500 living-donor liver transplant (LDLTs) are performed per year. Spain is the most DDLT-active country, and South Korea is the most LDLT-active country, performing 52 times as many and 5 times as many liver transplants per capita than Japan, respectively. Managing portal hypertension, ascites, hepatorenal syndrome, and spontaneous bacterial peritonitis is the key for bridging the interim period in patients waiting for liver transplantation. The Baveno VI consensus workshop recommendation is an important strategy for portal hypertension patients. International ascites club guidelines are other crucial strategies for ESLD patients. For a successful liver transplantation, multidisciplinary approach is essential to manage patients during both pre- and posttransplant periods. Regarding post-liver transplant patients, although liver transplantation resolves portal hypertension, a small-for-size graft in LDLT, acute rejection, and recurrence of the original liver disease may lead to newly developing or recurring portal hypertension. Further studies are needed to develop a management strategy for portal hypertension in pre- and post-liver transplant patients.

Keywords Baveno VI consensus · International ascites club guideline · Deceased-donor · Living-donor · Liver transplantation

J. Kaneko
Hepato-Billiary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

N. Kokudo (✉)
National Center for Global Health and Medicine, Tokyo, Japan
e-mail: nkokudo@hosp.ncgm.go.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_60

60.1 Introduction

Portal hypertension, a hemodynamic abnormality resulting from cirrhosis, is linked to ascites, hepatic encephalopathy, and variceal bleeding. Liver transplantation is the only curative treatment option for both portal hypertension and end-stage liver disease (ESLD). For successful liver transplantation, multidisciplinary approach is essential to manage patients during both pre- and posttransplantation periods: hepatologists manage the underlying liver disease and evaluate liver function, endoscopists and radiologists control esophagogastric varices, transplant surgeons finally evaluate the indications for transplantation and perform the liver transplantation, anesthesiologists and intensivists manage patients during and immediately after transplantation, and infectious disease experts control infectious processes in immunosuppressed patients. In this chapter, we first describe the current status of liver transplantation in the world and in Japan. Next, we focus on cutting-edge trends in managing portal hypertension and characteristic complications in ESLD patients who are on the liver transplant waiting list.

60.2 Current Status of Liver Transplantation in the World and in Japan

The first human deceased-donor liver transplantation (DDLT) was performed in the early 1960s by Thomas Starzl in the United States (USA) [1], and these days DDLT is commonly performed worldwide, with the USA performing the most liver transplants of any country. As of July 18, 2016, there were 14,619 patients on the waiting list for a liver transplant in the USA, based on the Organ Procurement and Transplantation Network data [2]. In 2015, 6768 recipients received a deceased-donor liver, and 359 recipients received a living-donor liver. The second and third most active countries are China and Brazil, and the number of liver transplants in each of these countries exceeds that in any European country. The number of liver transplants in Brazil has doubled over the past 7 years and has increased from 949 in 2005 to 1756 in 2014 [3]. According to data collected by Eurotransplant, an international nonprofit organization responsible for encouraging and coordinating organ transplants in Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia, 1707 patients were on the waiting list for a liver transplant at the end of June, 2016. In 2015, 1523 recipients in these countries received a deceased-donor liver, and 91 recipients received a living-donor liver [4]. In China, between 2000 and 2005, approximately 7477 transplants were performed, with 2970 transplants in 2005 alone [5]. During that period, sentenced convicts were the main organ source for transplantation. In 2010, China officially initiated a pilot program for voluntary organ donation to reduce the dependence on organs from executed convicts. Data from the China organ allocation and sharing system indicate that through September 17, 2011, 97 individuals donated organs, including 69 livers [6].

The first living-donor liver transplantation was attempted for a child by Raia and colleagues in Brazil in 1989, with the first successful case achieved by Strong and colleagues in 1990 [7, 8]. In 1992, Nagasue et al. reported the first pediatric LDLT in Japan [9]. Since 1994, when the Shinshu group reported the first successful adult-to-adult LDLT [10], the number of LDLT procedures for adult patients has increased around the world. Adult-to-adult LDLT is now an established treatment option for ESLD [10]. Approximately 400–500 liver transplants are performed per year in Japan. The number of patients on the waiting list for a DDLT in Japan on June 30, 2016, was 362. In 2015, 57 recipients received a deceased-donor liver [11]. In 2014, 418 recipients received a living-donor liver. Trotter and Cardenas considered that the low number of transplants performed in Japan is largely due to cultural prohibition against deceased-donor donation, as both Buddhism and Shintoism oppose deceased-organ donation. These views are slowly changing to a trend toward more acceptance [12].

LDLT is more common in Asian countries, and DDLT is the mainstay in Western countries. The liver transplantation activity per million population of each country is as follows [12]: DDLT activity in 2010 was 24.5 in Spain, 19 in Austria, 17 in the USA, 12.5 in Belgium, 11.5 in Italy, 10.5 in the UK, 9 in Germany, 8 in Brazil (2014), 7 in Australia, 6 in Korea, 5 in Hong Kong, 4 in Taiwan, and 0.47 in Japan (2015); and LDLT activity in 2010 was 0.7 in Spain, 3 in Belgium, 0.7 in Brazil (2014), 0.5 in Austria, 1.0 in the USA, 0.4 in Italy, 0.5 in the UK, 1.5 in Germany, 0.4 in Australia, 16 in Taiwan, 7 in Hong Kong, 17 in Korea, and 3.5 in Japan (2014) (Fig. 60.1). Spain is the most DDLT-active country and South Korea is the most LDLT-active country performing 52times as many and 5 times as many liver transplants per capita than Japan, respectively.

60.3 Allocation System

The Model for End-stage Liver Disease (MELD) score was initially developed to predict survival in patients with complications of portal hypertension undergoing elective placement of transjugular intrahepatic portosystemic shunts [13].

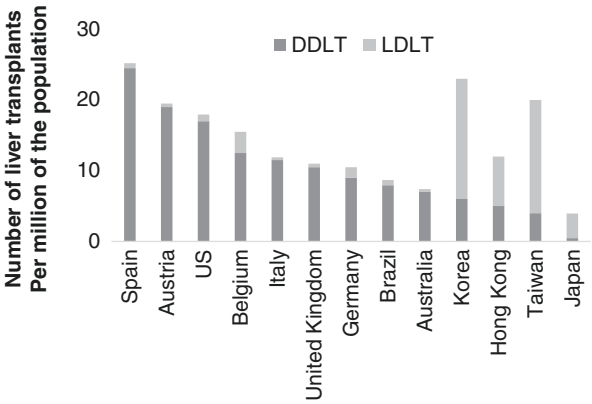


Fig. 60.1 The liver transplantation activity per million population of each country [12]. *US* United States, *DDLT* deceased-donor liver transplantation, *LDLT* living-donor liver transplantation

The MELD score is also an important stratification formula to predict the risk of death in patients on the waiting list for liver transplantation, and it has been used as a basic liver graft allocation system in the USA since 2002 [14]. The MELD score or a related system is now widely used for prioritizing ESLD patients on the liver transplant list. The MELD score is calculated based on the serum creatinine (mg/dL) and total bilirubin (mg/dL) concentrations, and the prothrombin time international normalized ratio. The pediatric end-stage liver disease (PELD) score, on the other hand, is calculated based on the albumin (g/dL) and total bilirubin (mg/dL) concentrations, the prothrombin time international normalized ratio, growth failure (based on sex, height, and weight), and age at listing. Allocation calculators are available on the following website "https://optn.transplant.hrsa.gov/resources/allocation-calculators/" [15].

Liver transplantation is less beneficial for patients with a MELD score of 15 or less [16]. Mortality risk of waiting list candidate and posttransplant recipient was studied among a cohort of 12,996 adult patients placed on the waiting list between 2001 and 2003. The recipients' mortality risk during the first posttransplant year is much higher for patients with lower MELD scores than for waiting list candidates (HR = 3.64 at MELD 6–11, HR = 2.35 at MELD 12–14; both $p < 0.001$) [16]. In Japan, the original scoring system based on the Child-Pugh score is used to stratify ESLD patients. The Japanese Liver Transplant Society is scheduled to begin using the MELD score to evaluate liver transplant candidates in 2018, which will make their allocation system more consistent with global standards.

60.4 Management of End-Stage Liver Disease Patients While on the Waiting List

60.4.1 Portal Hypertension

Managing portal hypertension is the key for bridging the interim period in patients waiting for a liver transplant. Generally, varices are present in 30–40% of compensated cirrhotic patients and 80% of decompensated cirrhotic patients. Varices have a similar prevalence rate in cirrhotic patients on the liver transplant waiting list to common cirrhotic patients [17]. A limitation of the predictive ability of MELD for transplantation patients is the clinical comorbidity of varices and variceal bleeding. Variceal bleeding remains an important cause of death in ESLD patients on the waiting list. Focusing on relation to Child-Pugh classification, gastroesophageal varices are present in approximately 40% of Child-Pugh A patients and 85% of Child-Pugh C patients [18]. Of patients with a low MELD score (<=20) on the waiting list for a liver transplant, 76% had varices and 39% died due to variceal bleeding [19]. There is still no worldwide consensus on the management of portal hypertension in patients waiting for a liver transplant. Cardenas and Gines made recommendations for prophylaxis against variceal bleeding in patients with cirrhosis awaiting

liver transplantation [20]. They classified the prophylaxis recommendations into primary and secondary practices (Table 60.1).

The Baveno VI consensus workshop developed recommendations for portal hypertension [21]. There were not many; however, liver transplantation was referred to in recommendation that related to Budd-Chiari syndrome or portal vein thrombosis. For example, Budd-Chiari syndrome/hepatic venous outflow tract obstruction should be managed according to a stepwise approach, including anticoagulation, angioplasty/thrombolysis, transjugular intrahepatic portosystemic shunt, and orthotopic liver transplantation at experienced centers (3b; B) (level of evidence from 1 = highest to 5 = lowest; grade of recommendation from A = strongest to D = weakest according to the Oxford System, [22]). Patients with a high prognostic index score (>=7) of Budd-Chiari syndrome with transjugular intrahepatic portosystemic shunt are likely to have a poor outcome, and thus orthotopic liver transplantation should be considered (3b; B), and liver transplantation should be considered in patients with manifestations refractory to the procedures (5; D). In terms of anticoagulation and portal vein thrombosis in cirrhosis, screening for portal vein thrombosis every 6 months is indicated for patients on the liver transplant waiting list (5;D). In this setting, the goal is to permit/facilitate liver transplant and reduce posttransplant mortality/morbidity, and anticoagulation should be maintained until transplantation to prevent rethrombosis (4; C). In untreated potential liver transplant candidates with portal vein thrombosis, follow-up with imaging every 3 months is recommended. Anticoagulation is recommended in case of progression (5; D). For patients who are not candidates for liver transplantation, there is currently no recommendation regarding anticoagulation treatment. Anticoagulation could be considered in selected cases (extension to superior mesenteric vein, known as a "strong" prothrombotic condition) (5; D). There were no other comments, however, regarding patients on the liver transplant waiting list.

Table 60.1 Recommendations for primary and secondary prophylaxis of variceal bleeding in patients with cirrhosis awaiting liver transplantation [20]

Primary prophylaxis
• Screen all patients on the waiting list with upper endoscopy
• No varices: No therapy indicated
But if the patients remain on the list, a repeat endoscopy should be performed in 1 year
• Small varices: Consider nonselective beta-blockers in patients with child B/C cirrhosis
• Medium/large varices: Beta-blockers or EVL may be used
Secondary prophylaxis
• Nonselective beta-blockers and EVL should be used for prevention of recurrent bleeding
• EVL should be done every 3–4 weeks until obliteration (approximately 3–4 sessions)
Surveillance endoscopy should be done 3 months after obliteration
• If previously on beta-blockers for primary prophylaxis, EVL should be added to drug treatment
Those previously treated with EVL and with no contraindication to beta-blockers should receive them
• TIPS is indicated in child A or B patients who rebleed despite combination therapy

EVL endoscopic variceal ligation, *TIPS* transjugular intrahepatic portosystemic shunt

The Japan Society for Portal Hypertension was established in 1994. With the increasing number of liver transplants being performed, the role of this society may become crucial. Collaboration between Japan and transplantation active countries may be the key to develop standardized protocols and procedures for managing portal hypertension in ESLD patients on waiting lists.

60.4.2 Ascites, Hepatorenal Syndrome, and Spontaneous Bacterial Peritonitis

In patients with severe cirrhosis, hepatorenal syndrome is the primary type of renal failure. Recent international ascites club guidelines recommend that patients with cirrhosis and ascites suspected of having an acute kidney injury should be managed as follows: (1) review drug chart—review of all medications, reduction or withdrawal of diuretic therapy, and withdrawal of all potentially nephrotoxic drugs, vasodilators, or nonsteroidal anti-inflammatory drugs; (2) plasma volume expansion in patients with clinically suspected hypovolemia; and (3) prompt recognition and early treatment of bacterial infections when diagnosed or strongly suspected. If no response after two consecutive days of diuretic withdrawal and plasma volume expansion with albumin, patients are diagnosed with hepatorenal syndrome, and treatment with a vasoconstrictor and added albumin are required [23]. Parenchymal renal disease is suspected when proteinuria exceeds 500 mg of protein/day and/or hematuria exceeds 50 red cells/high-power field [24]. Type 1 hepatorenal syndrome is defined as rapid progressive renal failure with doubling of the initial serum creatinine concentrations to a level greater than 2.5 mg/dL in less than 2 weeks. Type 1 hepatorenal syndrome has an extremely poor prognosis—less than 10% survival at 3 months [25]. Type 2 hepatorenal syndrome is defined as moderate renal failure (serum creatinine 1.5–2.5 mg/dL), with a stable or slowly progressive course. The prognosis of type 2 hepatorenal syndrome is also poor, with around 40% survival at 12 months [25]. Current guidelines recommend the administration of a vasopressin analogue in combination with albumin as the first-line therapeutic agent for hepatorenal syndrome [26]. The vasopressin analogue terlipressin is effective in approximately 40–50% of patients with hepatorenal syndrome. In Japan, the selective oral vasopressin V2 receptor antagonist tolvaptan is available to control ascites in patients with advanced cirrhosis.

Uncontrollable bacterial infection is considered a contraindication for liver transplantation and severe infection requires temporary removal from the waiting list. Spontaneous bacterial peritonitis accounts for 30% of the bacterial infections in cirrhotic patients. The 1-year survival probability after an episode of spontaneous bacterial peritonitis is only 40%. The diagnosis of spontaneous bacterial peritonitis is based on examination of the peritoneal fluid. When the polymorphonuclear count is greater than 250/mm, empiric antibiotic therapy is started. After successful treatment to stabilize spontaneous bacterial peritonitis, patients should be considered for liver transplantation as soon as possible.

60.4.3 Hyponatremia

Hyponatremia in ESLD is associated with a poor prognosis and a higher risk of hepatic encephalopathy. The MELD-Na score, which includes an evaluation of hyponatremia, is a new stratification formula to evaluate recipients for allocation [27]. Approximately 22% of patients with advanced cirrhosis and 50% of patients with refractory ascites or hepatorenal syndrome have serum sodium levels <130 meq/L. The selective oral vasopressin V2 receptor antagonist tolvaptan was reported to be useful for the treatment of hypervolemic hyponatremia [28]. Data regarding tolvaptan use in patients on the waiting list, however, are insufficient. Tolvaptan was temporarily approved in the USA for patients with cirrhosis and hyponatremia (serum sodium <125 meq/L), as well as for other conditions such as hypervolemic hyponatremia, but in January 2013, the US Food and Drug Administration warned of the potential risk of liver injury [29]. In Japan, the Ministry of Health, Labour, and Welfare approved tolvaptan for cirrhotic patients with ascites. Further studies are needed to clarify this issue.

60.5 Treatment of Portal Hypertension Post-liver Transplantation

In general, liver transplantation resolves portal hypertension. A small for size graft in LDLT, acute rejection, and recurrence of the original liver disease may lead to newly developing or recurring varices. Endoscopic surveillance may be important for patients who do not have an ideal postoperative course. Portal vein stenosis and thrombosis are uncommon complications after liver transplantation, with a frequency of around 3%. Occlusion of the portal vein immediately after transplantation has catastrophic consequences for the liver graft and leads to acute liver failure and eventually graft loss. Vascular stent placement into the portal vein is a favorable procedure for portal vein stenosis or thrombosis [30]. Although portal vein complications are asymptomatic in less than 50% of the cases, portal hypertension may cause various varices and require endoscopic treatment. There are several case reports regarding the management of posttransplantation shunt hepatic encephalopathy and the presence of a patent portosystemic shunt after liver transplantation due to portal occlusion or stenosis [31]. In one case report, a patient was successfully treated by placement of a self-expandable stent in the portal vein and the use of coils in the collateral veins. Although the portal vein was patent, the existence of portosystemic collaterals pretransplantation caused hepatic encephalopathy 10 months after transplantation despite a normal functioning liver graft. The patient was successfully treated by embolization of a large portosystemic shunt between the superior mesenteric vein and both gonadal veins [32]. In another case, a liver transplant recipient was successfully treated with percutaneous transhepatic coil embolization for the rupture of ectopic jejunum varices without portal

hypertension [33]. Further studies are needed to develop a management strategy for portal hypertension in post-liver transplant patients.

60.6 Conclusion

The world's longest-surviving liver transplant patient has lived for 42.7 years [34]. With the increasing number of both pre- and post-liver transplant patients worldwide, adequate management of portal hypertension and related diseases, refinement of the allocation system, and cooperation between specialists are essential for providing a favorable transplant outcome for patients with ESLD.

References

1. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. Surg Gynecol Obstet. 1963;117:659–76.
2. Organ Procurement and Transplantation Network data. http://optn.transplant.hrsa.gov. Accessed 18 July 2016.
3. Trotter JF, Cardenas A. Liver transplantation around the world. Liver Transpl. 2016;22(8):1059–61.
4. Eurotransplant. https://www.eurotransplant.org/cms/. Accessed 18 July 2016.
5. Wang H, Jiang W, Zhou Z, Long J, Li W, Fan ST. Liver transplantation in mainland China: the overview of CLTR 2011 annual scientific report. Hepatobiliary Surg Nutr. 2013;2(4):188–97.
6. Trey T, Halpern A, Singh MA. Organ transplantation and regulation in China. JAMA. 2011;306(17):1863–4; author reply 4.
7. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. N Engl J Med. 1990;322(21):1505–7.
8. Raia S, Nery JR, Mies S. Liver transplantation from live donors. Lancet. 1989;2(8661):497.
9. Nagasue N, Kohno H, Matsuo S, Yamanoi A, Uchida M, Takemoto Y, et al. Segmental (partial) liver transplantation from a living donor. Transplant Proc. 1992;24(5):1958–9.
10. Hashikura Y, Makuuchi M, Kawasaki S, Matsunami H, Ikegami T, Nakazawa Y, et al. Successful living-related partial liver transplantation to an adult patient. Lancet. 1994;343(8907):1233–4.
11. Japan OrganTransplant Network. https://www.jotnw.or.jp/english/index.html. Accessed 18 July 2016.
12. Chen CL, Kabiling CS, Concejero AM. Why does living donor liver transplantation flourish in Asia? Nat Rev Gastroenterol Hepatol. 2013;10(12):746–51.
13. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31(4):864–71.
14. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology. 2007;45(3):797–805.
15. MELD and PELD Calculator by Organ Procurement and Transplantation Network. https://optn.transplant.hrsa.gov/resources/allocation-calculators/about-meld-and-peld/. Accessed 18 July 2016.
16. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant. 2005;5(2):307–13.

17. Zaman A, Hapke R, Flora K, Rosen H, Benner K. Prevalence of upper and lower gastrointestinal tract findings in liver transplant candidates undergoing screening endoscopic evaluation. Am J Gastroenterol. 1999;94(4):895–9.
18. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46(3):922–38.
19. Wedd J, Bambha KM, Stotts M, Laskey H, Colmenero J, Gralla J, et al. Stage of cirrhosis predicts the risk of liver-related death in patients with low model for end-stage liver disease scores and cirrhosis awaiting liver transplantation. Liver Transpl. 2014;20(10):1193–201.
20. Cardenas A, Gines P. Management of patients with cirrhosis awaiting liver transplantation. Gut. 2011;60(3):412–21.
21. de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63(3):743–52.
22. Centre for Evidence-Based Medicine. http://www.cebm.net/. Accessed 10 Oct 2016.
23. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut. 2015;64(4):531–7.
24. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007;56(9):1310–8.
25. Alessandria C, Ozdogan O, Guevara M, Restuccia T, Jimenez W, Arroyo V, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. Hepatology. 2005;41(6):1282–9.
26. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53(3):397–417.
27. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology. 2006;130(6):1652–60.
28. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med. 2006;355(20):2099–112.
29. Samsca (tolvaptan): drug warning—potential risk of liver injury by U.S. Food and Drug Administration. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm336669.htm. Accessed 10 Oct 2016.
30. Cheng YF, Ou HY, Tsang LL, Yu CY, Huang TL, Chen TY, et al. Vascular stents in the management of portal venous complications in living donor liver transplantation. Am J Transplant. 2010;10(5):1276–83.
31. Arab JP, Meneses L, Perez RM, Arrese M, Benitez C. Hepatic encephalopathy in a liver transplant recipient with stable liver function. Hepatology. 2013;57(4):1672–4.
32. Herrero JI, Bilbao JI, Diaz ML, Alegre F, Inarrairaegui M, Pardo F, et al. Hepatic encephalopathy after liver transplantation in a patient with a normally functioning graft: treatment with embolization of portosystemic collaterals. Liver Transpl. 2009;15(1):111–4.
33. Abe S, Akamatsu N, Hoshikawa M, Shirata C, Sakamoto Y, Hasegawa K, et al. Ectopic jejunal variceal rupture in a liver transplant recipient successfully treated with percutaneous transhepatic coil embolization: a case report. Medicine. 2015;94(47):e2151.
34. Starzl TE. The long reach of liver transplantation. Nat Med. 2012;18(10):1489–92.

Part XI
Future Prospects on Portal Hypertension

Chapter 61
Future Prospects in the Treatment of Portal Hypertension

Takashi Tajiri, Hiroshi Yoshida, Hiroshi Makino, Atsushi Hirakata, Junji Ueda, Hideyuki Takata, Yasuhiro Mamada, Nobuhiko Taniai, and Eiji Uchida

Abstract Various complications, such as esophagogastric varices, ectopic varices, ascites, and hepatic encephalopathy, can occur in portal hypertension. Bleeding from esophagogastric or ectopic varices is the most critical complication of portal hypertension. In 1980, general rules for recording endoscopic findings of esophageal varices were initially proposed in Japan. Revised rules were proposed as "General Rules for Recording Endoscopic Findings of Esophagogastric Varices (1991)" and "General Rules for Recording Endoscopic Findings of Esophagogastric Varices (2010)." The revised rules are simpler and more straightforward than the former rules. In 2013, "General Rules for Study of Portal Hypertension" was proposed by the Japan Society for Portal Hypertension. These rules have widely been used in Japan and other countries.

Here, we review future prospects in the treatment of portal hypertension.

Keywords Future prospects · Portal hypertension

61.1 Introduction

Various complications, such as esophagogastric varices, ectopic varices, ascites, and hepatic encephalopathy, can occur in portal hypertension. Bleeding from esophagogastric or ectopic varices is the most critical complication of portal

T. Tajiri · H. Yoshida (✉) · Y. Mamada · E. Uchida
Department of Surgery, Nippon Medical School, Tokyo, Japan

H. Makino · A. Hirakata · J. Ueda · H. Takata
Department of Surgery, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan
e-mail: hiroshiy@nms.ac.jp

N. Taniai
Department of Surgery, Nippon Medical School Musashi Kosugi Hospital, Tokyo, Japan
e-mail: hiroshiy@nms.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_61

hypertension. Portal hypertension can arise from any condition interfering with blood flow at any level within the portal system.

Many years ago, surgery was the only treatment available for esophagogastric varices in Japan. Emergency operations were performed for the treatment of bleeding from esophagogastric varices, but many patients died of liver failure. In 1968, the Japan Society for the Study of Surgery for Portal Hypertension held its first meeting, after which it continued to hold annual meetings for 26 years. In the 1970s, techniques for interventional radiology (IVR) were developed and adopted, which improved the survival rates of patients with bleeding esophagogastric varices, and in the 1980s, endoscopic treatment further improved survival rates. In 1986, the Japan Society for the Study of Endoscopic Injection Sclerotherapy held its first meeting, and subsequently this society held meetings twice a year over a period of 9 years. Then in 1999, the Japan Society for Portal Hypertension held its first meeting, and this society has continued to hold annual meetings up to the present.

In 1980, general rules for recording endoscopic findings of esophageal varices were initially proposed in Japan [1]. Revised rules were proposed as "General Rules for Recording Endoscopic Findings of Esophagogastric Varices (1991)" [2, 3] and "General Rules for Recording Endoscopic Findings of Esophagogastric Varices (2010)" [4, 5]. The revised rules are simpler and more straightforward than the former rules. In 2013, "General rules for Study of Portal Hypertension" was proposed by the Japan Society for Portal Hypertension [6]. These rules have widely been used in Japan and other countries.

Here, we review future prospects in the treatment of portal hypertension.

61.2 Treatment Modalities for Portal Hypertension

Treatment modalities for various complications of portal hypertension include placement of a Sengstaken–Blakemore (SB) tube, self-expandable metallic stents, pharmacologic therapy, surgery, IVR, and endoscopic treatment. Optimal treatment of portal hypertension requires a strategy that takes into account the clinical stage of the disease and all the major variables that affect the risk of progression to the next stage and to death.

Currently, an SB tube [7] is used only as a temporary bridge to other strategies when other hemostatic treatments are unsuccessful. Recently, RCT showed that esophageal stents have greater efficacy with less serious adverse events than balloon tamponade [8]. In future, balloon tamponade or self-expandable metallic stents will be used rarely for the treatment of bleeding esophagogastric varices, but skill in tube or stent insertion should still be acquired.

Pharmacologic therapy for esophagogastric varices is generally applicable and can be started as soon as variceal hemorrhage is suspected. There are various drugs, such as nonselective β-blocker [9], vasopressin [10], somatostatin [10], and angiotensin II receptor blocker, for the treatment of portal hypertension [11]. Recently, pharmacologic therapy for the treatment of refractory ascites has been developed [12, 13]. In future, more effective drugs for the treatment of portal hypertension will

be developed. Pharmacologic therapy will be considered indispensable for portal hypertension [11, 13, 14].

Many years ago, surgery was the only treatment for bleeding esophagogastric varices, and several surgical procedures have been developed. Although the recurrence rate of esophagogastric varices is low, surgery is now reserved for refractory cases without severe liver damage. In future because it is invasive, the incidence of refractory cases will decrease, but the laparoscopic Hassab operation [15, 16] followed by endoscopic treatment will still be performed in selected patients.

Liver transplantation is a radical treatment for portal hypertension [17, 18]. In future, liver transplantation will be the first-line treatment in some countries for portal hypertension, although the shortage of donors in Japan means that it may not become the first-line treatment here. Selective shunt for refractory varices or nonselective shunt for refractory varices and ascites will be used as a temporary bridge to transplantation.

Transportal obliteration [19] and balloon-occluded retrograde transvenous obliteration (B-RTO) [20] are techniques used to embolize the collateral veins of the portal system in portal hypertension. Partial splenic embolization (PSE) [21] reduces inflow of the portal system. Insertion of a transjugular intrahepatic portosystemic shunt (TIPS) [22] increases outflow of the portal system. The IVR techniques of PSE and TIPS both reduce portal pressure.

In future, transportal obliteration will be used to treat refractory esophagogastric varices, ectopic varices, and portal systemic encephalopathy. B-RTO will be the first choice for the treatment of fundic varices, ectopic varices, and portal systemic encephalopathy. PSE will be performed as a supplemental treatment for portal hypertension. TIPS placement will be considered a salvage therapy for patients in whom standard medical therapy fails.

The combination of B-RTO and PSE will be a standard treatment for portal systemic encephalopathy. However, in refractory cases, devascularization of the portal systemic shunt will be necessary.

The incidence of refractory ascites will decrease, because most ascites will be controlled by pharmacologic therapy or paracentesis, or both. However, peritoneovenous shunt (Denver shunt) or TIPS will be considered a salvage therapy for patients with ascites in whom standard medical therapy fails.

Two endoscopic techniques are used to treat esophagogastric varices: endoscopic injection sclerotherapy (EIS) [23–27] and endoscopic variceal ligation (EVL) [28, 29].

EIS is useful to control acute bleeding from gastric or ectopic varices [23–27]. In the elective treatment of esophageal varices, intravariceal EIS obliterates both the interconnecting perforating veins and the veins feeding the esophageal varices. On the other hand, EVL is safe and simple because no sclerosant is used and is useful for controlling bleeding from esophageal varices. However, early recurrence of esophagogastric varices after EVL has been reported. Therefore, EIS should be performed after EVL in order to reduce recurrence. Brunner et al. reported that the treatment of acute variceal hemorrhage includes a combination of vasoactive drugs, antibiotics, and EVL [13]. The combination of IVR and endoscopic therapy will be highly effective and provides an alternative to surgery in patients with esophagogastric varices. In future, most of gastrointestinal varices could be treated mainly by

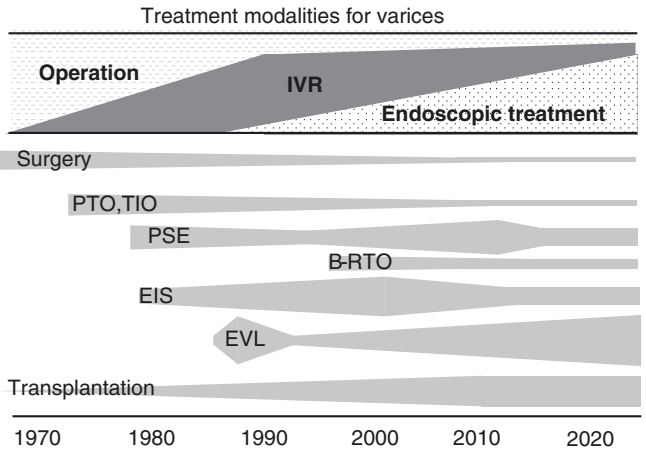


Fig. 61.1 Treatment modalities for varices. *IVR* interventional radiology, *PTO* percutaneous transhepatic obliteration, *TIO* transileocolic venous obliteration, *PSE* partial splenic embolization, *B-RTO* balloon-occluded retrograde transvenous obliteration, *EIS* endoscopic injection sclerotherapy, *EVL* endoscopic variceal ligation

endoscopic treatments. Vasoactive agents will be used routinely to manage variceal hemorrhage. Most bleeding esophageal varices will be treated with EVL. Endoscopic treatment using cyanoacrylate agents are used for acute bleeding from gastric or ectopic varices, whereas B-RTO will be a first-line treatment for fundic or ectopic varices. In cases of refractory varices, IVR or surgery will be performed (Fig. 61.1).

61.3 Future Research

61.3.1 Liver Cirrhosis

Liver cirrhosis is the main cause of portal hypertension. Advanced fibrosis may be present in chronic hepatitis B or C virus infection. Treatment of hepatitis B or C virus improves liver-related mortality in individuals with advanced fibrosis [30]. The cellular and molecular mechanism of liver fibrosis has been extensively studied, and new therapies based on these understandings are currently in early-phase clinical development [31].

61.3.2 Spleen

The spleen is a secondary lymphoid organ. Splenomegaly and hypersplenism occurred in portal hypertension. However, precise mechanisms remain poorly understood. Splenic characterization in the context of liver cirrhosis will be important for

the future management and treatment of liver cirrhosis. Future studies will be required to characterize the precise mechanistic pathways which mediate spleen and liver cross talk during disease progression from liver fibrosis to cirrhosis [32].

61.3.3 Noninvasive Assessment of Portal Hypertension

Ultrasound is a simple and noninvasive imaging modality available worldwide. Doppler measurement and contrast-enhanced ultrasound allow comprehensive assessment of portal hemodynamics. Recently, liver or spleen stiffness can be measured by elastography [33]. In future research, developments in digital technology will introduce various imaging modes.

References

1. The general rules for recording endoscopic findings on esophageal varices. Jpn J Surg. 1980;10(1):84–7.
2. Idezuki Y. General rules for recording endoscopic findings of esophagogastric varices (1991). Japanese Society for Portal Hypertension. World J Surg. 1995;19(3):420–2; discussion 3.
3. The Japan Society for Portal Hypertension. The general rules for study of portal hypertension. Tokyo: Kanehara Syuppan Co.; 1996.
4. Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc. 2010;22(1):1–9. https://doi.org/10.1111/j.1443-1661.2009.00929.x. DEN929 [pii].
5. The Japan Society for Portal Hypertension. The general rules for study of portal hypertension. 2nd ed. Tokyo: Kanehara and Co.; 2004. p. 37–50.
6. The Japan Society for Portal Hypertension. The general rules for study of portal hypertension. 62nd ed. Tokyo: Kanehara and Co.; 2013.
7. Sengstaken RW, Blakemore AH. Balloon tamponage for the control of hemorrhage from esophageal varices. Ann Surg. 1950;131(5):781–9.
8. Escorsell À, Pavel O, Cárdenas A, Morillas R, Llop E, Villanueva C, et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: a multicenter randomized, controlled trial. Hepatology. 2016;63(6):1957–67. https://doi.org/10.1002/hep.28360.
9. Abid S, Ali S, Baig MA, Waheed AA. Is it time to replace propranolol with carvedilol for portal hypertension? World J Gastrointest Endosc. 2015;7(5):532–9. https://doi.org/10.4253/wjge.v7.i5.532.
10. Wang C, Han J, Xiao L, Jin CE, Li DJ, Yang Z. Efficacy of vasopressin/terlipressin and somatostatin/octreotide for the prevention of early variceal rebleeding after the initial control of bleeding: a systematic review and meta-analysis. Hepatol Int. 2015;9(1):120–9. https://doi.org/10.1007/s12072-014-9594-9.
11. Berzigotti A, Bosch J. Pharmacologic management of portal hypertension. Clin Liver Dis. 2014;18(2):303–17. https://doi.org/10.1016/j.cld.2013.12.003.
12. Hayashi H, Beppu T, Okabe H, Kuroki H, Nakagawa S, Imai K, et al. Functional assessment versus conventional volumetric assessment in the prediction of operative outcomes after major hepatectomy. Surgery. 2015;157(1):20–6. https://doi.org/10.1016/j.surg.2014.06.013.
13. Brunner F, Berzigotti A, Bosch J. Prevention and treatment of variceal haemorrhage in 2017. Liver Int. 2017;37(Suppl 1):104–15. https://doi.org/10.1111/liv.13277.

14. D'Amico G, Pietrosi G, Tarantino I, Pagliaro L. Emergency sclerotherapy versus vasoactive drugs for variceal bleeding in cirrhosis: a Cochrane meta-analysis. Gastroenterology. 2003;124(5):1277–91. S0016508503002695 [pii].
15. Hassab MA. Nonshunt operations in portal hypertension without cirrhosis. Surg Gynecol Obstet. 1970;131(4):648–54.
16. Yamamoto J, Nagai M, Smith B, Tamaki S, Kubota T, Sasaki K, et al. Hand-assisted laparoscopic splenectomy and devascularization of the upper stomach in the management of gastric varices. World J Surg. 2006;30(8):1520–5. https://doi.org/10.1007/s00268-005-0243-2.
17. O'Leary JG, Lepe R, Davis GL. Indications for liver transplantation. Gastroenterology. 2008;134(6):1764–76. https://doi.org/10.1053/j.gastro.2008.02.028.
18. Hori T, Ogura Y, Onishi Y, Kamei H, Kurata N, Kainuma M, et al. Systemic hemodynamics in advanced cirrhosis: concerns during perioperative period of liver transplantation. World J Hepatol. 2016;8(25):1047–60. https://doi.org/10.4254/wjh.v8.i25.1047.
19. Kawai N, Minamiguchi H, Sato M, Ikoma A, Sanda H, Nakata K, et al. Percutaneous transportal outflow-vessel-occluded sclerotherapy for gastric varices unmanageable by balloon-occluded retrograde transvenous obliteration. Hepatol Res. 2013;43(4):430–5. https://doi.org/10.1111/j.1872-034X.2012.01078.x.
20. Kanagawa H, Mima S, Kouyama H, Gotoh K, Uchida T, Okuda K. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. J Gastroenterol Hepatol. 1996;11(1):51–8.
21. Hidaka H, Kokubu S, Saigenji K, Isobe Y, Maeda T. Restoration of thrombopoietin production after partial splenic embolization leads to resolution of thrombocytopenia in liver cirrhosis. Hepatol Res. 2002;23(4):265.
22. Narahara Y, Kanazawa H, Fukuda T, Matsushita Y, Harimoto H, Kidokoro H, et al. Transjugular intrahepatic portosystemic shunt versus paracentesis plus albumin in patients with refractory ascites who have good hepatic and renal function: a prospective randomized trial. J Gastroenterol. 2011;46(1):78–85. https://doi.org/10.1007/s00535-010-0282-9.
23. Lo GH, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. Hepatology. 2001;33(5):1060–4. https://doi.org/10.1053/jhep.2001.24116. S0270-9139(01)86668-4 [pii].
24. Kind R, Guglielmi A, Rodella L, Lombardo F, Catalano F, Ruzzenente A, et al. Bucrylate treatment of bleeding gastric varices: 12 years' experience. Endoscopy. 2000;32(7):512–9.
25. Huang YH, Yeh HZ, Chen GH, Chang CS, Wu CY, Poon SK, et al. Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacryl) injection: long-term efficacy and safety. Gastrointest Endosc. 2000;52(2):160–7. https://doi.org/10.1067/mge.2000.104976. S0016-5107(00)02407-X [pii].
26. Akahoshi T, Hashizume M, Shimabukuro R, Tanoue K, Tomikawa M, Okita K, et al. Long-term results of endoscopic Histoacryl injection sclerotherapy for gastric variceal bleeding: a 10-year experience. Surgery. 2002;131(1 Suppl):S176–81. a119501 [pii].
27. Sarin SK, Jain AK, Jain M, Gupta R. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. Am J Gastroenterol. 2002;97(4):1010–5. https://doi.org/10.1111/j.1572-0241.2002.05622.x.
28. Sarin SK, Govil A, Jain AK, Guptan RC, Issar SK, Jain M, et al. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. J Hepatol. 1997;26(4):826–32. S0168-8278(97)80248-6 [pii].
29. Bhargava DK, Pokharna R. Endoscopic variceal ligation versus endoscopic variceal ligation and endoscopic sclerotherapy: a prospective randomized study. Am J Gastroenterol. 1997;92(6):950–3.
30. Tamori A, Enomoto M, Kawada N. Recent advances in antiviral therapy for chronic hepatitis C. Mediat Inflamm. 2016;2016:6841628. https://doi.org/10.1155/2016/6841628.

31. Koyama Y, Brenner DA. New therapies for hepatic fibrosis. Clin Res Hepatol Gastroenterol. 2015;39(Suppl 1):S75–9. https://doi.org/10.1016/j.clinre.2015.06.011.
32. Li L, Duan M, Chen W, Jiang A, Li X, Yang J, et al. The spleen in liver cirrhosis: revisiting an old enemy with novel targets. J Transl Med. 2017;15(1):111. https://doi.org/10.1186/s12967-017-1214-8.
33. Maruyama H, Yokosuka O. Ultrasonography for noninvasive assessment of portal hypertension. Gut Liver. 2017;11:464. https://doi.org/10.5009/gnl16078.