Evaluation of Portal Circulation in Animal Model Experiments Using ^{99m}Tc -MIBI per Rectum[†]

Lanwen Xu CHEN, Norihisa TONAMI*, Shao-LIANG**, Xue-fen CHEN**,
Gang JIN**, Hui-Yang ZHAO** and Xingyu QING***

Department of Laboratory Animal, **Department of Nuclear Medicine,
***Department of Surgery,

Zhong-Shan Hospital, Shanghai Medical University
138, Yixue Road, Shanghai, 200022, China

*Department of Nuclear Medicine, Kanazawa University School of Medicine
Kanazawa-shi 920, Japan

Received November 7, 1994

A series of animal models for portal hypertension was prepared using the method of portal vein constriction. Four New Zealand domestic rabbits and six dogs were given portal imaging by per-rectal administration of ^{99m}Tc -MIBI and characteristics of quantitative portal hypertension were investigated. When the portal of domestic rabbits were constricted to 1/2, the heart/liver value (H/L) rose from 0.10 ± 0.04 to 0.57 ± 0.11 , and the heart shunt index (S.I.h) rose from 0.08 ± 0.03 to 0.36 ± 0.09 . These differences have significant meanings ($p < 0.05$). The shunt index for whole organs (S.I.w), however, only changed slightly. When the portal veins of the dogs were constricted to 1/3, 1/2 and 2/3 of their original widths, their H/L, S.I.h and S.I.w values rose in proportion respectively, and their correlation with the portal pressure measured during operation was very good. Immediately after the operation, the main feature observed was the compensational swelling of the spleen. One month later, image of the heart became even more conspicuous, demonstrating formation and establishment of the collateral circulation.

Key Words : portal hypertension, technetium-99m methoxy isobutyl
isonitrile, per-rectal portal imaging, animal experiment

1. Introduction

Evaluation of portal circulation is essential for the understanding of the pathological conditions of many liver diseases. It is also helpful in selecting the method of treatment for the patients with portal hypertension. In the past, it was reported that some radiopharmaceuticals have been employed to measure portal hypertension, such as $^{24}\text{Na}^1$, $\text{Na}^{131}\text{I}^{2-4}$, $^{133}\text{Xe}^5$, ^{99m}Tc pertechnetate⁶, and $^{13}\text{NH}_4^7$, but none of them could be accepted for routine clinical use. The main reason is that

these radiopharmaceuticals pass rapidly through the liver and do not stay there, making it extremely difficult to obtain the correct parameters.

Later on, it was reported that ^{201}Tl was employed⁸, but owing to its high cost and its limited source, it was still unfit for routine usage.

Recently ^{123}I -IMP was reported to be an agent for measurement of portal pressure⁹, but ^{123}I needs an accelerator in its production, and developing countries will find it difficult to employ it for routine usage. It is, therefore, imperative to discover a new tracer to determine quantitatively portal systemic shunting.

^{99m}Tc -MIBI is recognised to be one of the best imaging agent for myocardial perfusion imaging

[†] Address for correspondence : Norihisa Tonami, MD, Department of Nuclear Medicine, Kanazawa University School of Medicine, Kanazawa-shi 920, Japan.

at present. After administration of ^{99m}Tc -MIBI per rectum, it can be absorbed from the rectal membrane, concentrate in the liver and stay there for a comparatively long period. The radioactivity accumulated in the liver can further discrete to the gall-bladder, bile duct and intestines. In the systemic circulation ^{99m}Tc -MIBI can accumulate in myocardium, spleen, lungs, muscles and kidneys. We conducted research work on the measurement of portal pressure of ligated portal veins of animal models and developed a new method for determining portal pressure by administration of ^{99m}Tc -MIBI through rectum.

2. Materials and Methods

2.1 Preparation of experimental animal model

An initial transcolonic ^{99m}Tc -MIBI study was performed in a group of 4 normal New Zealand domestic rabbits and six normal dogs one week before surgery. They were then operated under anaesthetic and bacteria free conditions. Their portal veins were separated and the diameters and portal pressures were measured. The portal vein near the liver end was tied by thick silk threads so that the end diameter was $2/3$ to $1/3$ of the original values. It was observed that the portal pressure rose up at this time. After measurements of the pressures, the abdomens were closed for future experiments. The degree of constriction was $1/2$ for all four domestic rabbits, and $1/3$ for two dogs, $1/2$ for two, and $2/3$ for the remaining two.

2.2 Method of per-rectal portal imaging

After the animal was fast for 6 h, it was laid under gamma camera, with its abdomen facing upwards, the collimator of the camera covering the liver, heart, spleen and the lower portions of the lungs. A specially made catheter was inserted 20 cm into the upper part of the rectum, and a dose of 185 MBq (5 mCi) of ^{99m}Tc -MIBI was administered. Serial scintigrams were taken at 5 min

intervals for 2 or 3 h. Data were collected and stored by a computer. Regions of interest of the heart, liver, spleen, and lungs were drawn. After normalising, time-radioactivity curve was plotted for each region of interest.

2.3 Method of calculating indices

In order to determine quantitatively the portal systemic shunting conditions, we calculated the heart/liver ratio (H/L), the heart shunting index (S.I.h) and the shunting index for whole organs (S.I.w) according to the following equations:

$$\text{H/L} = \frac{\text{Counts of heart/pixel}}{\text{Counts of liver/pixel}}$$

$$\text{S.I.h} = \frac{\text{Counts of heart/pixel}}{\text{Counts of heart/pixel} + \text{liver/pixel}}$$

$$\text{S.I.w} = \frac{\text{Counts of heart/pixel} + \text{spleen/pixel} + \text{lung/pixel}}{\text{Counts of heart/pixel} + \text{spleen/pixel} + \text{lung/pixel} + \text{liver/pixel}}$$

3. Results

For normal animals, after per-rectal administration of ^{99m}Tc -MIBI, the radioactivity was seen in the liver, and liver image was apparent in 5 min, whereas the radioactivities of the heart, lungs and spleen remained low throughout the experiments (Fig. 1). Time-radio activity curve showed a low horizontal shape without rising trend (Fig. 2). Calculations according to the above-mentioned equations showed that for normal domestic rabbits and dogs, H/L values were 0.10 ± 0.04 and 0.07 ± 0.02 respectively and that S.I.h values were 0.08 ± 0.03 and 0.05 ± 0.02 respectively. Immediately after the operation of portal vein restriction, per-rectal portal imaging was carried out.

It was observed that the pressure has already risen up. Besides the appearance of radioactivity of the liver, heart and spleen also showed distinct radioactivity and became more distinct as time went on. Image of the heart could be seen and the spleen was distinctly enlarged (Fig. 3). The time-

Fig. 1 Image of a normal dog before operation. 90 min after transrectal administration of $^{99m}\text{Tc-MIBI}$. The liver is clearly visualized, while other organs are not visualized.

Fig. 2 Time-activity curve of the heart of a normal dog before operation.

radioactivity curve of the heart showed an increasing shape (Fig. 4). H/L and S.I. values also rose up significantly.

Table 1 shows the portal pressure and width of the portal vein of the experimental dog before and after operation, and their calculated indices. Portal pressure increases with the extent of constriction of the portal vein. So are the H/L and S.I. indices. H/L, S.I.h and S.I.w increase proportionally with portal pressure, the correlation of S.I.w being the best one. One month later, portal imaging was repeated on the experimental animal

Fig. 3 Image of the same dog immediately after operation. 90 min after transrectal administration of $^{99m}\text{Tc-MIBI}$. Besides the liver, heart and spleen are also visualized. The spleen is enlarged.

Fig. 4 Time-activity curve of the heart in the same dog after constriction of 1/2 of the portal vein.

models which had received normal food. It was found that the images of the heart were clearer, but the images of the spleen were smaller than those of one month ago after the operation (Fig. 5). Values of H/L and S.I.h were higher than those immediately after operation, whereas the S.I.w value had no significant changes (Table 1).

Fifteen minutes to 2 or 3 h after the administra-

Fig. 5 Image of the same dog one month after constriction of 1/2 of the portal vein.

The heart became clearer and the spleen became smaller compared with those of one month ago.

tion of pharmaceuticals, values of H/L and S.I. remained basically steady. Their difference is insignificant ($p > 0.05$). Three hours later, H/L and S.I. values rose significantly.

4. Discussion

In the past, most of portal hypertension experiments in animal models were carried out by chronic bile duct ligation¹⁰⁾. Normally 4 to 6 weeks were needed for the formation of liver cirrhosis before it could be used for experiment and the increase of portal pressure during this

period could not be measured directly, unless the abdomen was operated again. The advantage of chronic bile duct ligation is the closer coincidence between disease process and formation process of the portal hypertension. We adopted the method of portal vein constriction, which directly causes the pressure rise at the extremity of the constriction. The method is comparatively simple, and it is easier to observe the formation and establishment of the collateral circulation as a result of the pressure rise. Furthermore, it is possible to vary the diameter of the constricted portal vein according to various demands so as to control the extent of pressure rise, thus forming a series of pressure gradient for observation purposes. The drawback of this method is that it does not coincide with the formation process of human diseases.

It was possible to observe the impact of the increase of portal pressure on the blood flow dynamics immediately after the operation. Since it is impossible to establish the collaterals from portal to systemic circulation, the blood flow of the spleen increases. As a result, the spleen is filled with blood and enlarges, causing a reduction of the pressure rise of the portal vein. As time passes on, the collateral circulation is established and work, portal pressure is decreasing gradually. Therefore, after one month after operation, the swelling of the spleen was not so significant as that on the day of operation, and the myocardial

Table 1 Related indexes in dogs with portal vein constriction

No.	Pre-operation					During operation		Immediately after operation			One month later after operation		
	Portal pressure (mmH ₂ O)	Portal width (cm)	H/L	S.I.h (%)	S.I.w (%)	Degree of constriction	Portal pressure (mmH ₂ O)	H/L	S.I.h (%)	S.I.w (%)	H/L	S.I.h (%)	S.I.w (%)
1	6.2	1.0	0.06	4	10	1/3	17.2	0.12	10	34	0.24	19	35
2	8.6	1.2	0.07	5	11	1/3	14.1	0.11	10	32	0.25	20	34
3	10.2	1.0	0.09	7	12	1/2	25.1	0.15	13	43	0.32	24	41
4	9.8	0.9	0.08	6	11	1/2	27.8	0.24	19	47	0.45	31	48
5	8.8	1.1	0.07	6	10	2/3	30.3	0.27	23	59	0.51	33	52
6	11.3	1.2	0.09	8	12	2/3	29.4	0.25	20	43	0.47	32	47

visualization was apparant. This explains the difference of images seen on the day of operation and one month later. Similarly, since H/L and S.I.h only reflect the ratio of portal blood flow shunting, these values rose up a little bit without significancy on the day of operation, whereas one month later they rose significantly. On the contrary, S.I.w rose significantly on the day of operation, but did not change much after one month. This demonstrates that the introduction of S.I.w is very important for the understanding of the full picture of portal systemic shunting. This research work, through a series of portal hypertension gradient observation and calculation of related indices, has proved that it seems to be possible to quantitatively determine the portal pressure. Among these parameters, the correlation of S.I.w with actual pressure is the best one.

Based on the fact that parameters remained basically steady between 15 min and 2 – 3 h after administration of pharmaceuticals, the method of measurement can be further simplified in actual practice.

References

- 1) Deterling, R. A., Powers S. R. and Bhonslay, S. B. : *Surg. Forum*, 5, 193–200 (1954)
- 2) Blondheim, S.H., Ben-Porath, M and Ben Ishai, Z : *Isr. Med. J.*, 17, 222–224 (1958)
- 3) Lewitus, Z. and Laor, J. : *J. Med. Sci. Isr.*, 4, 41–46 (1968)
- 4) Steinberg, M., Marner, I. and Rasmussen, J. W. : *Scand. J. Gastroenterol.*, 9, 73–79 (1974)
- 5) Castell, D. O., Grace, N. D., Wennar, M. H., Chalmer, T. C. and Moore, E. W. : *Gastroenterology*, 57, 533–541 (1969)
- 6) Shiomi, S., Kuroki, T., Kurai, O., Kobayashi, K., Ikeoka, N., Monna, T. and Ochi, H. : *J. Nucl. Med.*, 29, 460–465 (1988)
- 7) Hazenberg, H. J. A., Gips, C. H., Beekhuis, H. and Vaalburg, W. : *Acta Hepato-Gastroenterol.*, 23, 308–318 (1976)
- 8) Tonami, N., Nakajima, K., Hisada, K., Tanaka, N. and Kobayashi, K. : *J. Nucl. Med.*, 23, 965–972 (1982)
- 9) Kashiwagi, T., Azuma, M., Ikawa, T., Takehara, T., Matsuda, H., Yoshioka, H., Mitsutani, N., Koizumi, T. and Kimura, K. : *Radiology*, 169, 137–140 (1988)
- 10) Koblik, P. D., Hornof, W. J., Yen, C. K., Komtebedde, J., Breznock, E. and Fisher, P. : *J. Nucl. Med.*, 32, 124–129 (1991)

要 旨

 ^{99m}Tc -MIBI 経直腸投与による動物モデルでの門脈循環の評価

許 蘭 文, 利波紀久*, 陳 紹 亮**, 陳 雪 芬**, 金 剛**
趙 惠 揚**, 秦 新 裕***

上海医科大学実験動物教室, **核医学教室, ***外科教室

138, Yixue Road, Shanghei 200022, 中国

*金沢大学医学部核医学教室

920 金沢市宝町 13-1

門脈狭窄の方法を用いて門脈圧亢進症の動物モデルを作製した。4羽のニュージーランド家兎と6匹の犬に ^{99m}Tc -MIBI を経直腸的に投与し門脈イメージングを行い定量的に門脈亢進の特徴を検討した。家兎の門脈を 1/2 に狭窄すると ^{99m}Tc -MIBI の心/肝摂取比は 0.10 ± 0.04 から 0.05 ± 0.11 に、心短絡指標（単位ピクセル当たりの心/心+肝カウント）は 0.08 ± 0.03 から 0.36 ± 0.09 に有意（ $p < 0.05$ ）に増加した。しかし、全臓器の短絡指標（単位ピクセル当たりの心+脾+肝/心+脾+肺+肝カウント）の変化はわずかであった。犬の門脈を 1/3, 1/2, 2/3 と狭窄を増すにつれてそれぞれの指標は増加し、狭窄術直後に測定した門脈圧と非常に良く相関した。狭窄術直後の主な特徴として代償的な脾の腫張がみられた。1か月後には経直腸イメージで心描画はより顕著となり短絡路の形成を示した。