Index of convexity: A novel liver function index using Tc-GSA scintigraphy

Kenji Miki, Yuichi Matsui, Masanori Teruya, Michio Kaminishi, Norihiro Kokudo

Abstract

AIM: To investigate the clinical usefulness of a newly developed index, the "index of convexity (IOC)", for evaluating liver functional reserve using technetium-99m-diethylenetriaminepentaacetic acid-galactosyl-human serum albumin (Tc-GSA scintigraphy).

METHODS: In total, 349 patients underwent Tc-GSA scintigraphy. Dynamic planner images were obtained, and time activity curves of the liver and heart were generated and analyzed. Our focus was on the convex shape of the liver accumulation curve. We developed a method for evaluating the extent of convexity and calculated an index that we named the IOC. Clearance index and receptor index were also calculated. The correlations between each GSA index with other liver function tests and liver histopathology were evaluated.

RESULTS: Among the 3 indices generated by Tc-GSA, the IOC had the highest correlation with all other liver function tests (indocyanine green R15, albumin, prothrombin time, cholinesterase level, platelet count, and total bilirubin level). IOC can also differentiate between normal liver, chronic hepatitis, and liver cirrhosis with highest F ratio among GSA indices as determined by one-way analysis of variance. Receiver operating characteristic analysis demonstrated high diagnostic performance of IOC in the diagnosis of cirrhosis.

CONCLUSION: IOC is a very simple and reliable index for assessing liver functional reserve, which may prove to be useful in combination with the indocyanine green test for preoperative assessment of hepatic resection.

© 2013 Baishideng. All rights reserved.

Key words: Liver functional reserve; Preoperative assessment; Technetium-99m-diethylenetriaminepentaacetic acid-galactosyl-human serum albumin; Liver cirrhosis; Hepatectomy

INTRODUCTION

Preoperative assessment of liver functional reserve is crucial for hepatobiliary surgeons. Technetium-99m-diethylenetriaminepentaacetic acid-galactosyl-human serum albumin (Tc-GSA) is a radiopharmaceutical developed for evaluating liver function\(^1,2\), and has been widely used for preoperative assessment\(^3,4\). This asialoglycoprotein (ASGP) analogue is specifically taken up by hepatocytes\(^5\), and its rate of accumulation in the liver can be evaluated using a gamma camera\(^6\). The liver accumulation process can be assessed by generating a time activ-
ity curve (TAC) from dynamic planer images. Several indices of liver function have been reported through the analysis of dynamic planer images\(^{[7-11]}\). Clearance index (HH15) and receptor index (LHL15) have been widely used for almost 20 years\(^{[7,8]}\), as they are easy to calculate. On the other hand, R\(_{\text{max}}\) or R\(_{\text{total}}\) are calculated using kinetic model analysis\(^{[9,10]}\), which is highly complex and therefore not widely used. Index LU15 requires measurement of the radioactivity of the injection syringe\(^{[11]}\), and the Ki index requires curve-fitting software\(^{[4]}\). The use of both of these methods is limited. Although HH15 and LHL15 have been widely used for a long time, both indices have several problems\(^{[12,13]}\). HH15 uses only the radioactivity counts of the heart pool, which is very low compared to liver counts. This index can thus be influenced by counts in the liver through scatter effects or body movements. Index LHL15 is directly influenced by the manner in which the heart regions of interest (ROI) is drawn, generating inter-operator or inter-institutional differences\(^{[13,14]}\).

To overcome these problems, we focus on the shape of the liver TAC. Liver TACs have a convex shape in patients with good liver function. In contrast, liver TACs increase in a linear manner in patients with poor liver function. We developed a method for evaluating the convexity of the liver TAC and calculated an index that we have named the index of convexity (IOC).

In this study, we evaluated the significance and usefulness of this index for the assessment of the liver functional reserve.

**MATERIALS AND METHODS**

**Patients**

This study included 349 patients who received Tc-GSA scintigraphy at the University of Tokyo Hospital or Showa General Hospital between 1998 and 2011. Of these patients, 239 had hepatocellular carcinomas, 34 had metastatic liver tumors, and 39 had cholangiocarcinomas. Others were diagnosed with miscellaneous diseases. Liver histology in 236 patients confirmed a diagnosis of chronic hepatitis (48 patients), normal liver (45 patients), and liver cirrhosis (143 patients).

**Tc-GSA scintigraphy**

All patients received 3 mg of Tc-GSA (185 MBq) intravenously. After the injection, dynamic images were obtained with the patient in a supine position using a large-field view gamma camera. Digital images were acquired at 30 s intervals for 30 min. TACs were generated by drawing ROI over the whole liver [L(t)] and heart [H(t)] on the digital images.

**Conventional parameters**

The HH15 and LHL15 were defined as follows: HH15 = H(15)/H(3); LHL15 = L(15)/(L(15) + L(3)).

**IOC**

The convexity of the liver TAC was evaluated by an index defined as follows: \(\Delta ABC\) was drawn over the liver TAC, where A and B were placed on the TAC at the data points corresponding to 3 min and 27 min after injection, respectively. Therefore, the coordinates of A, B, and C were A[3, L(3)], B[27, L(27)], and C[3, L(27)], respectively. D and E were set as the mid points of lines AB and BC, respectively. F was defined as the intersection of lines AB and BC, respectively. F was defined as the intersection of line DE and arc AB (Figure 1).

The better the liver function, the higher is the index \(\text{IOC}\). High \(\text{IOC}\) values indicate good liver function.

Figure 1  Representative time activity curves of a liver with good function (top) and poor function (bottom). \(\Delta ABC\) was drawn over the liver curve between the data points at 3 min and 27 min after injection, respectively. The midpoint of lines AB and BC is F. The ratio of the length of DF to the length of DE is defined as index of convexity (IOC). High IOC values indicate good liver function.

**Other liver function tests**

The indocyanine green (ICG) test was carried out, and 2 parameters (ICG R15 and ICG K value) were calculated using the standard methods. Serum albumin level (mg/dL), choline esterase level (IU/L), total bilirubin concentration (mg/dL), platelet counts (\(\times 10^3/\text{mm}^3\)), and prothrombin time (%) were also measured.

**Statistical analysis**

Correlations between the 3 parameters of the Tc-GSA study (HH15, LHL15 and IOC) and other liver function
A strong correlation between the 2 parameters is observed ($r = -0.761$). IOC: Index of convexity; ICG R15: Indocyanine green retention rate at 15 min.

Table 1  Spearman’s rank correlation coefficients

| Index      | IOC   | HH15  | LHL15 | ICG R15 |
|------------|-------|-------|-------|---------|
| Albumin    | 0.611 | 0.56  | -0.582| -0.538  |
| PT         | 0.556 | 0.555 | -0.521| -0.549  |
| Platelets  | 0.607 | 0.571 | -0.572| -0.465  |
| ChE        | 0.548 | 0.481 | -0.496| -0.481  |
| T. Bil     | -0.552| -0.508| 0.51  | 0.53    |

ICG R15: Indocyanine green retention rate at 15 min; PT: Prothrombin time; ChE: Choline esterase level; T. Bil: Total bilirubin concentration; IOC: Index of convexity; HH15: Clearance index; LHL15: Receptor index.

tests were estimated as Spearman’s rank correlations. The differences in each Tc-GSA parameter between the 3 groups (normal liver, chronic hepatitis, and liver cirrhosis) were evaluated by one-way analysis of variance (ANOVA). The diagnostic performance for the diagnosis of cirrhosis was evaluated by receiver operating characteristic (ROC) analysis.

RESULTS

Spearman’s rank correlation coefficients are listed in Table 1. IOC showed stronger correlations than the other conventional indices of HH15 and LHL15. In particular, the IOC has a strong correlation to ICG R15 values compared to HH15 or LHL15 (Figure 2). The correlation coefficient between IOC and ICG R15 was statistically higher than that between HH15 and ICG R15 and that between LHL15 and ICG R15.

The results of one-way ANOVA also showed that IOC was significantly different between background liver groups with the highest $F$ ratio (Table 2).

We performed ROC analysis to evaluate the diagnostic performance of IOC in diagnosing cirrhosis (Figure 3). The area under the curve (AUC) of ROC curves for IOC, HH15 and LHL15 were 0.851, 0.660 and 0.681, respectively. However, these differences were not statistically significant.

DISCUSSION

In this study, we developed a novel index to evaluate liver function using the dynamic images of Tc-GSA scintigraphy. This index is very simple to calculate and has stronger correlations to other liver function tests than do conventional indices such as HH15 or LHL15. This index also has a high diagnostic performance rating for diagnosing liver cirrhosis. IOC would thus be very useful to hepatobiliary surgeons in assessing preoperative liver function.

Tc-GSA is an ASGP analogue labeled with a radioisotope and developed for the assessment of liver functional reserve. Tc-GSA scintigraphy for assessing liver function has several benefits to consider. First, accumulation of Tc-GSA in the liver can be monitored continuously through dynamic planer images. The kinetics of ASGP have been investigated in detail in animals and humans[6,9,10], and several kinetic parameters have been proposed as candidates for indices of liver function[8,9,10]. Second, regional accumulation of Tc-GSA in the liver was measured separately to evaluate regional liver function via single photon emission computed tomography images[17-19], which can be used for the assessment of regional liver function after portal vein embolization[20,21]. Although many parameters of Tc-GSA scintigraphy have been reported, only HH15 and LHL15 are used widely.
Despite their widespread use, we found that both of these indices showed only moderate correlations to other liver functions, and we encountered some cases with a discrepancy between the values of both indices and their liver histology or liver functions\textsuperscript{[12,13]}. Since the TAC of the heart is influenced by background radiation or radioactivity in the liver adjacent to the heart, indicated Tc-GSA concentrations may deviate from the actual blood concentrations\textsuperscript{[22]}. HH15, using only TAC of the heart and ignoring liver accumulation, is not suitable for the ideal index. LHL15 has been shown to be directly influenced by the manner in which the ROI is drawn over the heart\textsuperscript{[13,14]}. The LHL15 index value was also found to be influenced by the shape of the liver and the size of the heart. These observations suggest that HH15 and LHL15 indices are prone to several measurement errors.

To overcome these problems, we focused on the shape of the liver accumulation curve. The shape of the liver accumulation curve seems universally consistent, even if the patients are stout or their liver is deformed.

The convexity of the liver curve seems to be a specific feature of good liver function. The liver curve increased rapidly and afterwards reaches a plateau in the case of good liver function. In contrast, the liver curve increases linearly throughout the examination period, with no plateau, in patients with poor liver function. In order to evaluate the convexity of the liver curve, we calculated the ratio of the length of line DF to line DE as described in Figure 1. IOC decreases as liver function deteriorates. This index correlated very strongly to other liver function tests, including ICG. IOC can be calculated quite easily as calculations require liver radioactivity data at only 3 time points. Results of one-way ANOVA indicate that IOC has a higher correlation to liver histology than does HH15 or LHL15. In fact, IOC seemed to be superior to HH15 or LHL15 in the diagnosis of liver cirrhosis as indicated by ROC analysis, although the differences between the AUC of ROC curves for IOC, HH15, and LHL15 were not statistically significant.

Makuuchi et al proposed that the criteria determining the extent of liver resection include ascites volume, bilirubin levels, and ICG tests\textsuperscript{[23]}. Since then, the ICG test has been widely used in Japan for the preoperative assessment of liver functional reserve. It is well known that hyperbilirubinemia and large port-systemic shunts interfere with the results of ICG tests\textsuperscript{[24,25]}. In addition, some patients are intolerant of ICG\textsuperscript{[26]}. We have encountered many cases with large discrepancies between ICG results and conventional liver function tests. In these cases, Tc-GSA scintigraphy plays a complementary role in deciding on surgical procedures. In this study, IOC showed a stronger correlation with conventional liver function tests than did the ICG test. IOC is a simple and reliable index that is superior to HH15 and LHL15 indices and is a valuable parameter exceeding ICG tests in the preoperative assessment of liver functional reserve. We analyzed the Tc-GSA data retrospectively in this study. In order to prove the usefulness of this index, further prospective studies should be undertaken.

REFERENCES
1. Torizuka K, Ha-Kawa SK, Ikekubo K, Suga Y, Tanaka Y, Hino M, Ito H, Yamamoto K, Yonekura Y. [Phase I clinical study on 99mTc-GSA, a new agent for functional imaging of the liver]. Kaku Igaku. 1991; 28: 1321-1331 [PMID: 1770847]
2. Torizuka K, Ha-Kawa SK, Kudo M, Kitagawa S, Kubota Y, Tanaka Y, Hino M, Ikekubo K. [Phase II clinical study on 99mTc-GSA, a new agent for functional imaging of the liver]. Kaku Igaku. 1992; 29: 85-95 [PMID: 1578824]
3. Kwon AH, Ha-Kawa SK, Uetsuji S, Kamiyama Y, Tanaka Y. Use of technetium 99m diethylenetriamine-pentaacetic acid-galactosyl-human serum albumin liver scintigraphy in the evaluation of preoperative and postoperative hepatic functional reserve for hepatocellular carcinoma. [Surgery]. 1995; 117: 429-434 [PMID: 7716725 DOI: 10.1016/S0039-6060(05)8063-7]
4. Mitsuomori N, Nagaiga Y, Kimoto S, Akaki S, Togami I, Takeda Y, Joa I, Hikari Y. Preoperative evaluation of hepatic functional reserve following hepatectomy by technetium-99m galactosyl human serum albumin liver scintigraphy and...
Miki K et al. IOC: A new index of Tc-GSA

computed tomography. Eur J Nucl Med 1998; 25: 1377-1382 [PMID: 9818276 DOI: 10.1007/s002590050311]

5 Morell AG, Gregoriadis G, Scheinberg IH, Hickman J, Ashwell G. The role of sialic acid in determining the survival of glycoproteins in the circulation. J Biol Chem 1971; 246: 1461-1467 [PMID: 5545089]

6 Stadalnik RC, Vera DR, Woodle ES, Trudeau WL, Porter BA, Ward RE, Krohn KA, O’Grady LF. Technetium-99m NGA functional hepatic imaging: preliminary clinical experience. J Nucl Med 1985; 26: 1233-1242 [PMID: 2997417]

7 Kudo M, Todo A, Ikekubo K, Hino M, Yonekura Y, Yamamoto T, Torizuka K. Functional hepatic imaging with receptor-binding radiopharmaceutical: clinical potential as a measure of functioning hepatocyte mass. Gastroenterol Jpn 1991; 26: 734-741 [PMID: 1662653]

8 Kudo M, Todo A, Ikekubo K, Hino M. Receptor index via hepatic asialoglycoprotein receptor imaging: correlation with chronic hepatocellular damage. Am J Gastroenterol 1992; 87: 865-870 [PMID: 1615940]

9 Ha-Kawa SK, Tanaka Y. A quantitative model of technetium-99m-DTPA-galactosyl-HSA for the assessment of hepatic blood flow and hepatic binding receptor. J Nucl Med 1991, 32: 2233-2240 [PMID: 1744708]

10 Miki K, Kubota K, Kokudo N, Inoue Y, Bandai Y, Makuuchi M. Asialoglycoprotein receptor and hepatic blood flow using technetium-99m-DTPA-galactosyl human serum albumin. J Nucl Med 1997; 38: 1798-1807 [PMID: 9374359]

11 Koizumi K, Uchiyama G, Arai T, Aino T, Yoda Y. A new liver functional study using Tc-99m DTPA-galactosyl human serum albumin: evaluation of the validity of several functional parameters. Ann Nucl Med 1992; 6: 83-87 [PMID: 1320389]

12 Kokudo N, Vera DR, Makuuchi M. Clinical application of Tc-GSA. Nucl Med Biol 2003; 30: 845-849 [PMID: 14698788]

13 Nakajima K, Kinuya K, Mizutani Y, Hwang EH, Michigishi T, Tonami N, Kobayashi K. Simple scintigraphic parameters with Tc-99m galactosyl human serum albumin for clinical staging of chronic hepatocellular dysfunction. Ann Nucl Med 1999; 13: 5-11 [PMID: 10202942]

14 Koizumi M, Yamada Y, Nomura E, Takiguchi T, Kokudo N. An easy and reproducible semi-automatic method for the evaluation of 99mTc-galactosyl human serum albumin. Ann Nucl Med 1997; 11: 345-348 [PMID: 9460529]

15 Schwartz AL, Fridovich SE, Lodish HF. Kinetics of internalization and recycling of the asialoglycoprotein receptor in a hepatoma cell line. J Biol Chem 1982; 257: 4220-4237 [PMID: 6276829]

16 Sawamura T, Nakada H, Hazama H, Shoizaki Y, Sameshima Y, Tashiro Y. Hypersialoglycoproteinemia in patients with chronic liver diseases and/or liver cell carcinoma. Asialo-glycoprotein receptor in cirrhosis and liver cell carcinoma. Gastroenterology 1994; 87: 1217-1221 [PMID: 6092193]

17 Matsuzaki S, Onda M, Tajiri T, Kim DY. Hepatic lobar differences in progression of chronic liver disease: correlation of asialo-glycoprotein scintigraphy and hepatic functional reserve. Hepatology 1997; 25: 828-832 [PMID: 9096583 DOI: 10.1002/hep.10250407]

18 Akagi S, Mitsumori A, Kanazawa S, Togami I, Takeda Y, Hirai Y. Lobar decrease in 99mTc-GSA accumulation in hilar cholangiocarcinoma. J Nucl Med 1999; 40: 394-398 [PMID: 10086701]

19 Hwang EH, Taki J, Shuke N, Nakajima K, Kinuya S, Konishi S, Michigishi T, Aburano T, Tonami N. Preoperative assessment of residual hepatic functional reserve using 99mTc-DTPA-galactosyl-human serum albumin dynamic SPECT. J Nucl Med 1999; 40: 1644-1651 [PMID: 10520704]

20 Sugiyama M, Komatani A, Hosoya T, Yamaguchi K. Response to percutaneous transhepatic portal embolization: new proposed parameters by 99mTc-GSA SPECT and their usefulness in prognostic estimation after hepatectomy. J Nucl Med 2000; 41: 421-425 [PMID: 10716313]

21 Beppu T, Hayashi H, Okabe H, Masuda T, Mima K, Otao R, Chikamoto A, Doi K, Ishiko T, Takamori H, Yoshida M, Shiraiishi S, Yamashita Y, Baba H. Liver functional volumetry for portal vein embolization using a newly developed 99mTc-galactosyl human serum albumin scintigraphy SPECT-computed tomography fusion system. J Gastroenterol 2011; 46: 938-943 [PMID: 21523415 DOI: 10.1007/s00535-011-0406-x]

22 Ha-Kawa SK, Kojima M, Suga Y, Kurokawa H, Itagaki Y, Tanaka Y. [Dose estimation of Tc-99m-DTPA-galactosyl-human serum albumin (Tc-99m-GSA) in the blood with non-linear regression method]. Kaku Igaku 1991; 28: 425-428 [PMID: 1880977]

23 Miyagawa S, Makuuchi M, Kawasaki S, Kakazu T. Criterias for sale hepatic resection. Ann J Surg 1995; 169: 589-594 [PMID: 7771622 DOI: 10.1016/S0002-9610(99)80227-X]

24 Stockmann M, Malinowski M, Lock JF, Seehofer D, Neuhaus P. Factors influencing the indocyanine green (ICG) test: additional impact of acute cholestasis. Hepatogastroenterology 2009; 56: 734-738 [PMID: 19621693]

25 Miyamoto Y, Oho K, Kumamoto M, Toyonaga A, Sata M. Balloon-occluded retrograde transvenous obliteration improves liver function in patients with cirrhosis and portal hypertension. J Gastroenterol Hepatol 2003; 18: 934-942 [PMID: 12859723 DOI: 10.1046/j.1440-1746.2003.03087.x]

26 Okuda K, Okahashi H, Musha H, Kotoeda K, Abe H, Tanikawa K. Marked delay in indocyanine green plasma clearance with a near-normal bromosulphthalein retention test: a constitutional abnormality? Gut 1976; 17: 588-594 [PMID: 976796 DOI: 10.1136/gut.17.8.588]

P- Reviewers Zocco MA, Cheng KS, Tandon RK
S- Editor Jiang L L- Editor A E- Editor Xiong L