Nuclear gastroenterology: novel techniques in clinical and experimental gastrointestinal mobility, IBD and hepatology

Bennink, R.J.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 16

Summary and conclusions

Roelof Bennink

Department of Nuclear Medicine
(Academic Medical Center Amsterdam, The Netherlands)
Chapter 16

Most of the clinical manifestations of gastrointestinal (GI) disease reflect abnormal function. Dysphagia, dyspepsia, change in bowel habit, abdominal pain, GI bleeding, and jaundice are all manifestations of disturbed physiology. Whereas abnormal anatomy is usually best investigated by endoscopy, conventional radiology, ultrasound or computed tomography (CT), some functional abnormalities are better defined and explored by radionuclide techniques. Research in GI motility, IBD and hepatology is making quantum leap progression increasing the demand for noninvasive validation of hypotheses and techniques. Therefore, the aim of this thesis was to further characterize existing nuclear medicine techniques in the evolving field of gastroenterology and to explore novel applications and techniques for clinical and experimental use in human studies and animal experiments.

Gastrointestinal motility

Radionuclide gastric emptying studies are widely used for clinical and research purposes. The normal values for these studies are generally based on all-male or mixed populations, because it has been assumed that men and women have identical rates of gastric emptying. Over the last 10 years, however, it has become increasingly evident that women have slower gastric emptying rates for solids and possibly also for liquids. The aims of the study presented in chapter 2 were (1) to confirm the difference in gastric emptying for solid and liquid test meal between healthy men and women and (2) to investigate the origin of this difference in absence of pathology by studying regional gastric emptying and antral motility. We demonstrated that gastric emptying of solids is significantly slower in women as compared to men. In contrast with pathological situations such as idiopathic or diabetes mellitus gastroparesis, where antral motor activity is affected, the antral motor activity does not seem to play a major role in the gender difference. In our opinion, the gastric fundus is also responsible for delaying the gastric emptying in females.

Dual-isotope scintigraphy is the gold standard for evaluation of gastric emptying. With the addition of powerful tools such as regional gastric emptying and dynamic antral
Summary and conclusions

Scintigraphy the test is even more informative without increasing the radiation burden excessively. For routine clinical purposes, each nuclear medicine facility should define 2 separate sets of normal gastric emptying reference values for men and premenopausal women. As regards future experimental work, we believe it is of major interest that investigations are carried out separately for men and women. This might clarify some of the contradictions in the literature, possible caused by different ratios of men and women in study protocols.

When evaluating small-bowel transit as part of an entire bowel transit protocol, determination of the 10% small bowel transit time (SBTT) for solid test meal could be different for male and female patients because gastric emptying is slower in healthy premenopausal women than in men. Therefore, the purpose of the study presented in chapter 3 was to define normal values of small-bowel transit in men and women, and to assess if there is a gender difference, or a difference between solids and liquids. Unlike gastric emptying, the SBTT of solids and liquids is not significantly different, nor was a significant difference for gender found in healthy volunteers. Determination of the orocecal transit time (OCTT) seems to be the simplest and most accurate approach to measure SBTT with scintigraphy, because of less dependence on gastric emptying, even though no significant difference could be demonstrated in healthy controls. Whether or not, defining the 10%SBTT as well will be helpful in differentiating between gastric and small bowel dysmotility in idiopathic gastroparesis remains to be elucidated. Finally, our observations confirm that an $^{111}$In-DTPA labeled liquid test meal can also be used for the determination of colon transit in a single imaging, whole-gut study protocol since ileocecal transfer occurs as a bolus phenomenon.

Scintigraphy is usually considered the reference technique for measuring the OCTT. Several drawbacks, however, limit its application in routine practice. Expensive equipment, time and specialized personnel are required, and the use of radioactive isotopes is associated with some irradiation (<3 mSv). It is not preferable to repeat the technique at short intervals in children, and in pregnant women the use of this technique should be avoided completely. Therefore, it was the aim of the study presented in chapter 4 to investigate the validity of the lactulose-$^{14}$Cureide (LU) breath test (LUBT) by direct comparison with a well-established method, namely scintigraphy using a
Chapter 16

$^{99m}$Tc-sulfur colloid labeled test meal. The highly significant correlation of OCTT measured using LUBT and the scintigraphically determined OCTT in these healthy volunteers shows that the breath test could be a valid alternative for scintigraphy.

The use of mouse models has increased in gastrointestinal (GI) research, particularly in GI oncology and GI immunology. In contrast, GI motility research would benefit from further development and application of mouse models. The aims of the study presented in chapter 5 were: (1) to adapt a routine pinhole gamma camera system, suitable for murine gastric-emptying scintigraphy without the need of sedation or invasive parabiotic preparation, (2) to validate murine gastric-emptying scintigraphy by comparing it to an established technique such as phenol red recovery, and (3) to determine normal values for solid and liquid gastric emptying and evaluate effects of multiple handling or earlier sedation and/or analgesia on gastric emptying. It has been shown that pinhole gastric-emptying scintigraphy in small laboratory animals allows accurate, noninvasive measurement of gastric emptying of both liquids and solids. It correlates well with the gold standard, phenol red, but requires significantly fewer laboratory animals and provides more information. Finally, it allows serial measurements in the same animal, making this technique suitable to evaluate the effects of pharmacologic or other interventions on gastric emptying within the same animal.

An application of the model described and validated in chapter 5 is illustrated in chapter 6. In this study, the aim was to show in a murine model for postoperative ileus that leukocyte infiltrates recruited in the intestinal muscularis by selective small-intestinal manipulation affect the motility of parts of the gastrointestinal tract, distant from the site of manipulation, by triggering an inhibitory neural pathway. Gastrointestinal motility was successfully assessed with pinhole gastric emptying-scintigraphy in mice.

Measurement of the gastric accommodation response to meal intake is technically difficult and available techniques have methodological drawbacks. The current gold standard for the measurement of accommodation is the gastric barostat, involving the introduction of a balloon into the gastric fundus. In addition to the discomfort associated with this invasive and time-consuming procedure, the presence of a balloon in the
Summary and conclusions

Stomach has been shown to cause dilatation of the antrum as a result of meal displacement and induction of exaggerated proximal gastric relaxation. The aim of the study presented in chapter 7 was to refine a recently described scintigraphic method, limiting the radiation dose applied and increasing possible postinjection imaging time span without losing image quality, so that sequential (multiple measurements within 1 test) and repetitive (measurements before and after treatment) measurements within 1 subject become possible without increasing radiation burden. It has been shown that noninvasive measurement of gastric volume with a reduced dose of pertechnetate is feasible without losing image quality. This noninvasive technique enables repeated and serial measurement of gastric volume response to a test meal, a process that is potential useful for characterization and follow-up of dyspeptic patients with and without drug intervention.

The volumes measured by gastric volume scintigraphy (GVS) will reflect intragastric content such as gastric secretions, swallowed air and ingested foods or liquids. Based on these assumptions, we hypothesized in chapter 8 that in the absence of a barostat balloon, GVS will largely detect the volume effect of meal ingestion and will be a rather insensitive tool to detect fundic relaxation. To test this hypothesis, the ability to detect fundic relaxation of comparable magnitude evoked by meal ingestion or glucagon was compared between the 2 techniques performed at separate days. We concluded that GVS is able to detect changes in gastric volume in a noninvasive manner. However, our data suggest that GVS, in the absence of a distending force, is less suitable than the gastric barostat to detect gastric relaxation and rather detects the volume of the intragastric contents after meal intake. These findings question the role of GVS as a tool to detect gastric relaxation or impaired accommodation and imply that further validation is required, for instance by using a larger test meal or drink test protocols.
Chapter 16

Inflammatory bowel disease

Ulcerative colitis (UC) is a chronic inflammatory bowel disease accompanied by frequent acute exacerbations. It is usually diagnosed by rectosigmoidoscopy, colonoscopy or double-contrast barium enema. Colonoscopic and contrast radiographic procedures have inherent disadvantages and can be cause of severe complications. However, knowing the severity of disease is important for estimating the intensity of anti-inflammatory therapy and the risk of complications. The aim of the study presented in chapter 9 was to determine if $^{99m}$Tc-HMPAO labeled WBC scintigraphy could be an alternative to endoscopy with biopsy to determine the extent and the severity of the disease in these critically ill patients. It was demonstrated that disease severity can be determined adequately by planar WBC scintigraphy in patients with a severe attack of UC. Because the presence and severity of disease correlates well with histologic findings, it is possible to assess disease activity and extent with WBC scintigraphy without the need for colonoscopy. This could decrease the number and severity of complications in already critically ill patients.

Treatment of UC is mainly based on corticosteroids, administered orally, parenterally or rectally. A rapid and sustained response is usually seen within a few days following initiation of treatment. However, the overall rate of steroid treatment failure in acute exacerbations of UC remains high, and 20-30% of patients ultimately require surgery. Prediction of the long-term prognosis of UC at the time of diagnosis and early identification of which patients with a severe exacerbation will not respond to therapy remains difficult. The aim of the study presented in chapter 10 was to determine if WBC scintigraphy can predict early treatment failure in patients with acute attacks of UC. Repeated WBC scintigraphy seems able to predict therapy resistance in UC within 1 wk after start of treatment. This technique provides a noninvasive and reliable tool to monitor therapy in ulcerative colitis and depict nonresponders in an early stage where intensifying therapy or changing management or ultimately colectomy is possible without losing valuable time and increasing risk of dangerous complications.
Summary and conclusions

In chapter 11, it has been shown that the concept of pinhole SPECT using a rotating object and a fixed collimated camera-head is technically feasible and enables SPECT imaging in small animals. Using this procedure, we circumvent the problem of mechanical shift and unknown instabilities in a practical, easy-to-use and low-cost environment. Therefore, pinhole SPECT may be used more extensively for the assessment of in vivo uptake of radioligands in small animals and may replace many in vitro experiments, reducing the number of animals needed for experiments.

Although the initiating events of IBD are still unknown, increasing evidence indicates that mucosal CD4⁺ T cells activated by enteric bacteria initiate and perpetuate the inflammation in genetically susceptible individuals. Aberrant (excessive or inappropriate) homing of these cells to mucosal sites is believed to be a central element in the pathogenesis of IBD. For investigating these homing patterns, a noninvasive technique, able to assess lymphocyte recirculation and kinetics in the follow-up of experimental treatment for IBD, would not only benefit longitudinal studies, but also reduce the number of animals required to test. Therefore, the aim of the study presented in chapter 12 was to construct and validate an animal model for IBD, in which intestinal lymphocyte homing can be monitored noninvasively in vivo by means of pinhole SPECT. Our results indicate that lymphocyte homing can be assessed in vivo by means of dedicated animal pinhole SPECT using a technique that enables serial measurement of specific cell trafficking in TNBS colitis. This technique provides temporal insight in the disease process, and yields potential of in vivo evaluation of novel anti-inflammatory strategies in IBD. In the study presented in chapter 13, we used dedicated animal SPECT for assessment of radioactive labeled ¹¹¹In-oxinate purified T helper lymphocyte homing to the gut in TNBS-induced experimental colitis in mice. Furthermore, we applied this technique to study blockade of intestinal lymphocyte influx in TNBS colitis with an anti-α4 integrin antibody. The results of this study indicate that SPECT of ¹¹¹In labeled purified lymphocytes is a straightforward and reliable technique to assess lymphocyte migration to the colon in experimental colitis and the radioactive uptake ratio of the colon can be used as a parameter of disease activity in vivo. Blockade of lymphocyte homing by an anti-α4 antibody was detected by SPECT in vivo and could be
confirmed by planar pinhole scintigraphy of isolated colons. Therefore, SPECT can improve the preclinical development of drugs that intervene with lymphocyte migration to the inflamed intestine.

**Liver disease**

Preoperative assessment of liver function is used to estimate the outcome of major liver surgery. To date, the most frequently used test for evaluating preoperative liver function is the indocyanine green clearance (ICG) test. This test, requiring intravenous injection and multiple blood samples, provides indirect measurement of global liver function only. Alternatively, $^{99m}$Tc-labeled iminodiacetic acid (IDA) analogues, transported in blood by binding to albumin and with a hepatic uptake similar to ICG, can be used for hepatobiliary scintigraphy (HBS) in the assessment of liver function. HBS, requiring a single intravenous injection, provides visual and quantitative information of global and regional liver function as well as information on excretory biliary function. The aim of the study presented in chapter 14 was to examine the correlation of the ICG clearance test with the uptake of $^{99m}$Tc-mebrofenin as determined from the blood as well as from scintigraphical assessment. The data presented in this study show that $^{99m}$Tc-mebrofenin uptake rate as assessed by scintigraphy correlates well with ICG clearance and is a valid method for determining the liver function. Additional morphological information obtained from HBS provides valuable information on localization of liver segments with inferior function and/or bile pooling in obstructed liver segments.

The maximum extent of resection compatible with a safe postoperative outcome remains unknown, but it is generally believed that the risk for perioperative complications increases when the remnant liver volume is too small. Therefore, preoperative assessment of hepatic function and remnant liver volume (RLV) is advocated. Preoperative and remnant liver volumes can be accurately estimated with CT. However, most strategies evaluating preoperative hepatic function reserve and estimating the remnant liver volume rely on a homogeneous liver function. Unlike patients undergoing liver resection for metastatic cancer or benign liver conditions, patients with
Summary and conclusions

Hepatocellular carcinoma or obstructing tumors like cholangiocarcinoma may have underlying chronic liver disease or cholestasis with primary or secondary impaired total or segmental liver function. There is a good correlation of the preoperative $^{99m}$Tc-mebrofenin liver uptake rate and the ICG clearance test in patients scheduled for major liver surgery. Therefore, the aim of the study presented in chapter 15 was to assess total and regional liver function before and after major liver surgery and to compare scintigraphic results with volumetric data and ICG clearance test results. Furthermore, the correlation of the immediate postoperative remnant liver function (RLF) predicted on preoperative scintigraphy and measured 24 h after surgery with scintigraphy was assessed. Finally, the relation between liver function regeneration determined with HBS and volumetry was assessed. It has been shown that HBS offers a unique combination of functional liver uptake and excretion assessment with the ability to determine the preoperative liver function reserve and to estimate the RLF preoperatively. Determination of the RLF instead of the RLV might clarify some of the discrepancies observed in the literature between RLV and clinical outcome in patients with a nonhomogenous liver function. Finally, it has been shown that liver function regeneration can be monitored using HBS.
Chapter 16

Nuclear Gastroenterology

Scintigraphy has more potential than the routine clinical investigations currently available in most nuclear medicine facilities. The current applicability of scintigraphic methods in gastroenterology is larger and includes for instance detection and quantification of gastroesophageal and enterogastric reflux, esophageal clearance, gastric emptying, small bowel and colonic transit, calculous and acalculous biliary disorders, localization of ectopic gastric mucosa in a Meckel’s diverticulum, localization of sites of GI hemorrhage and identification of sites of inflammation in the GI tract.

This thesis is an illustration of the ability of nuclear medicine to adapt to changing clinical and experimental needs for investigation of physiological and pathophysiological processes. The ability of nuclear medicine to image and quantify these processes without interference or introducing nonphysiological devices is a serious advantage. Furthermore, the possibility of repetitive measurements in laboratory animals potentially reduces the number of animals needed for experiments in which animals would have to be sacrificed for the measurement act. Despite the possible advantages of these nuclear medicine techniques, radiation exposure should always be accounted for in the ultimate decision whether to use techniques involving radiation.

Nuclear gastroenterology remains an important part of nuclear medicine. In a dynamic nuclear medicine environment, with multiple challenges like PET, receptor imaging, apoptosis and radioimmunotherapy, modern nuclear techniques prove to be useful for clinical and experimental gastroenterology. Nuclear medicine physicians have to be aware of basic nuclear gastroenterology and its evolution. Therefore, the opportunity to acquire this specific knowledge in training and by continuing education should remain. Profound knowledge of all aspects of nuclear medicine, including nuclear gastroenterology, is a key to improving patient management and advances in medical research.