„BABEŞ – BOLYAI" UNIVERSITY CLUJ – NAPOCA

FACULTY OF ENVIRONMENTAL SCIENCE AND ENGINEERING

BIOPHYSICAL AND RADIOLOGICAL PROTECTION ASPECTS IN DYNAMIC INVESTIGATIONS OF LIVER IN NUCLEAR MEDICINE

DOCTORAL THESIS ABSTRACT

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Key words:
Nuclear Medicine, dynamic hepatobiliary scintigraphy, liver scintigraphy, transrectal portal scintigraphy, radiotracer, radiopharmaceutical, Tetrofosmin, Nanocoll

***The figure numbering is identical to the one found in the thesis proper.

Introduction

The discovery of natural radioactivity in the year 1896 has marked the beginning of a new scientific field – Nuclear physics.

As research progressed, several applications of Nuclear physics have emerged, influencing almost every branch of human activity; medicine was one of the first to enjoy the benefits of the new discoveries.

The need for more and more accurate diagnosis fueled the desire to non-invasively visualize various organs and internal structures of the human organism, leading in the past fifty years to an astounding evolution of a certain field, established over the years under the name of Medical imaging.

One of the methods ensuring this purpose is the (radioactive) marking of internal organs with an isotope and their subsequent visualization with specialized detection equipment; the method was perfected following the early years of Nuclear physics, when the physical properties of radionuclides were established.

Nuclear Medicine is a branch of medical imaging which involves the visualization of internal organs by radionuclide marking followed by image reconstruction (ensured by gamma radiation detection equipment); it has evolved alongside the diversification of radiation detection devices and the identification of isotopes having adequate properties and has imposed itself by in vivo and in vitro diagnostic techniques.

Since 1996, I have joined the team of the Nuclear Medicine Laboratory within the Clinical Hospital for Adults in Cluj-Napoca, lead by Prof. Sabin Cotul, MD.

I had the honour to be initiated as a Nuclear Medicine physician by the first persons to set up such a unit in Cluj-Napoca, which was to become a genuine school in the field.

Our laboratory has always been open to novelty and to continuous research, which helped sustain Nuclear Medicine as an important branch of medical imaging, despite the extensive development of non-invasive investigation techniques developed in the past years.

This fact is illustrated by our endeavor to continue studying the data yielded by dynamic hepatic scintigraphy, performed in Romania in our laboratory alone at present and offering functional as well as morphological information of the liver.

The tradition of research on the data from dynamic liver scintigraphy was initiated by Prof. Sabin Cotul, MD, whose studies were published in several books as well as national and international journals.

This research was continued by Dr. Mircea Dragoteanu with a series of national and international articles and publications; I had the honor to coauthor some of these.

The difficulty to perform and interpret the dynamic scintigraphic examinations, depending on a synchronized team, has lead in time to a decrease of the number of units performing them.

As a consequence, the radiopharmaceutical market has limited its offer of products designed for liver scintigraphy.

The constant request for dynamic liver scintigraphy, however, has prompted me to study the possibility to perform it using non-conventionally the radiopharmaceuticals available at present in our country.

This study aims to reintroduce in clinical practice two types of hepatic scintigraphic investigations: dynamic hepatobiliary scintigraphy and radiocolloid liver scintigraphy.

I have therefore studied the bibliography in the field, the pharmacokinetics, chemical composition, as well as dosimetry information of products available to us and have consequently established a working protocol.

We took special care all through the study to observe the radioprotection norms and the economic aspects of dynamic hepatic scintigraphy performed with the newly-proposed pharmaceuticals.

All the scintigraphic images reproduced in this paper were obtained in our laboratory by the same team mentioned above lead by dr. Mircea Dragoteanu, PhD, laboratory coordinator, a Nuclear Medicine consultant.

The image interpretation and medical counseling were performed by dr. Mircea Dragoteanu.

The present work has contributed not only to the reinstatement of above-mentioned investigations in clinical practice, but also to develop a study of the transrectal portoscintigraphic curves – in what concerns the biophysical phenomena and the calculation of the portocaval shunt index.

I. Nuclear Medicine equipment

I.1 Scintillation camera - setup

A scintillation camera is a combination of devices allowing the detection of gamma radiation emitted by a source and also the image reconstruction of that source by identifying the spatial distribution of the points the radiation was emitted from; it is composed of the radiation detector proper and the auxiliary installation. (Mateescu Ghe., 2000)

The technique for obtaining scintigraphic images results in the bidimensional or tridimensional reconstruction (such as in tomographies) of the image of an organ or tissue; this is possible following the marking of the tissue or organ with a radiopharmaceutical product (RPP) which is biodistributed in a certain volume.

The detector is the site of interaction between the incident particle, which delivers its energy partially or totally, while the auxiliary installation transforms this information in an accessible measure (electric current or pulses).

I.2 Principles of medical generators - The ^{99}Mo / ^{99m}Tc generator

Generators are produced starting at the idea that the disintegration of a high number of radionuclides does not lead in one stage to the stable element, but in a succession of steps, each with its own half-life, corresponding to the newly obtained radionuclide. (Mateescu Ghe., 2000)

The initial radionuclide is called “parent radionuclide”, the ones resulting from intermediary steps are called “daughter radionuclides”, with the last of the chain considered as the stable element (characterized by a long half-life).

The medical generator is a system constantly producing a gamma radioactive isotope obtained as a daughter nuclide and having a relatively short half-life. (Mateescu Ghe., 2000)

A radioactive series characterizing a medical generator is represented as follows:

$X_1 \to X_2 \to X_3 \; X_i$ - radionuclides composing the radioactive series

$\lambda_1 \; \lambda_2 \; \lambda_i$ - corresponding decay constants

In this series the third nucleus is stable. (Mateescu Ghe., 2000)

Considering the corresponding decay constants, the status of a medical generator preserves a balance where $\lambda_1 < \lambda_2$.

In 1958, Walter Tucker and Margaret Green have realized the first ^{99}Mo / ^{99m}Tc generator, which became in time the most used medical generator because of its optimal physical properties, but also because of its tendency to form organic compounds of technetium with different organ tropisms.

The technology for realizing medical generators is a relatively simple one and is based on the elution of a chromatographic band made of a porous material (usually alumina - Al_2O_3), which absorbs the parent isotope; the medically important isotope (the “daughter”) is then extracted by flushing with an organic solvent (usually normal saline – a NaCl solution in distilled water in 9‰ concentration).

$$^{235}U(n, fis) \to {}^{99}_{42}Mo \xrightarrow{\beta^-(90\%)} {}^{99m}_{43}Tc \xrightarrow{\gamma(100\%)\,140keV} {}^{99}_{43}Tc \xrightarrow{\beta^-} {}^{99}_{44}Ru$$

$^{99m}_{43}Tc$ has a half-life of 6,05 h and decays in up to 98,6% by emitting gamma quanta of 140keV energy.

Equipment used for the present paper

I.3 The SPECT Orbiter Siemens scintillation camera

The SPECT Orbiter Siemens scintillation camera in our laboratory was manufactured by Siemens Medical Systems Inc. USA in 1994.

Hepatic scintigraphies: dynamic, static, tomographic – the object of study of this PhD thesis – require a Hi Res Paralel collimator with calibrated slots for the 140KeV energy.

The NaI scintillation crystal impurified with Tl is 40 cm in diameter, with 37 photomultipliers on its surface.

The spectrometric system allows for a width of the energy peak of ± 5%.

Acquisition of the scintigraphic images as well as data processing were performed on a Power MacIntosh computer, with ICON software, intended for this type of medical applications (image acquisition and processing). (Technical textbook of the Pho Gamma SPECT Orbiter Siemens scintillation camera)

II. Characteristics of radiopharmaceutical products

The gamma radioactive isotope reaches the target organ bound to a pharmaceutical compound having tropism for the intended organ or tissue. (Cotul S, 1988)

The marked chemicals become radiopharmaceutical compounds (RPC) and can be used both for diagnostic investigations and for therapy.

The morphological and functional data obtained with the RPC depend of its pharmacokinetics and its tropism for certain organs and is a valuable source of information for reaching a correct diagnosis.

The biophysical transport and fixation of RPC to the organ of interest will determine the types of investigations available for that particular organ. The main mechanisms involved in the penetration of certain RPC in tissues are:

1. Active transport – the RPC contains substances usually metabolized in the intended organ;

2. Passive transport – requires no energy consumption and takes place down the concentration gradient (from the compartment with higher concentration to the one of lower concentration).

Passive transport includes the microtransport of small molecules, ions, gases but also the macrotransport of larger particles.

Simple diffusion, favoured diffusion, transport through ion channels and pores are all types of microtransport.

Macrotransport includes phagocytosis and pinocytosis.

III. Classical scintigraphy of the liver

III.1 Dynamic hepatobiliary scintigraphy

The main principle at the basis of dynamic hepatobiliary scintigraphy is tracing the pharmacokinetics of certain liposoluble substances and organic anions, which cannot be cleared renally; these are actively taken up from the circulation by hepatocytes and then follow the evacuation of the bile, competing with it, through the intrahepatic biliary ducts, gallbladder and small bowel. (Cotul S, 1988; Grigorescu M, 2009)

The chemical designed for classic hepatobiliary scintigraphy is HIDA: diethylphenyl-carbamoylmethyl/-iminodiacetic acid, which, after binding to ^{99m}Tc forms a substance that can be injected to patients. (HIDA information sheet)

The normal dynamic curves indicate a progressive increase in activity per area unit in the liver, followed by a decrease in activity when the bile starts to accumulate in the gallbladder.

The increase in activity in the bowel takes place when radioactive-marked bile reaches it after leaving the gallbladder through the extrahepatic ducts.

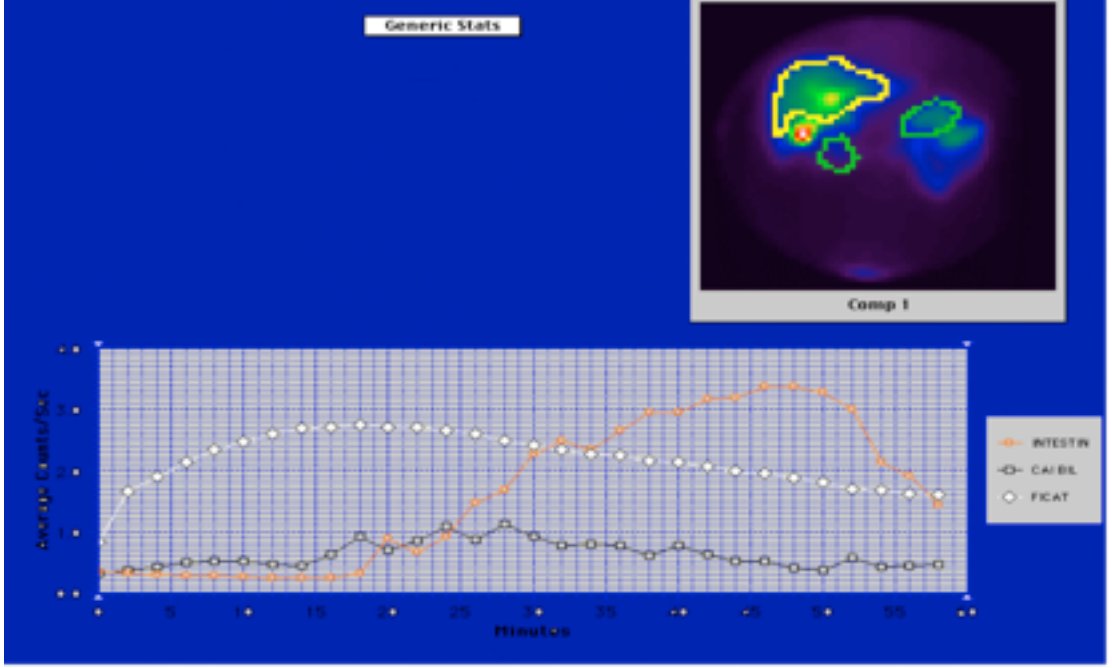


Fig. III 3.1 ^{99m}Tc -HIDA dynamic hepatobiliary scintigraphy with graphic representation of the dynamic curves obtained for liver, biliary ducts and bowel

III.2 Hepatic scintigraphy using ^{99m}Tc - sodium phytate

The principle at the basis of this investigation is the ability of liver Kupffer cells to extract from circulation the particled substances reaching the liver and to absorb them by phagocytosis.

Phagocytosis is a passive macrotransport phenomenon involving the interception of colloidal particles by the macrophages in a certain system.

^{99m}Tc - sodium phytate becomes colloidal in vivo (after intravenous injection), due to binding to Ca^{2+} ions, and it is rapidly extracted from circulation by the liver Kupffer cells. (FYTON – technical sheet)

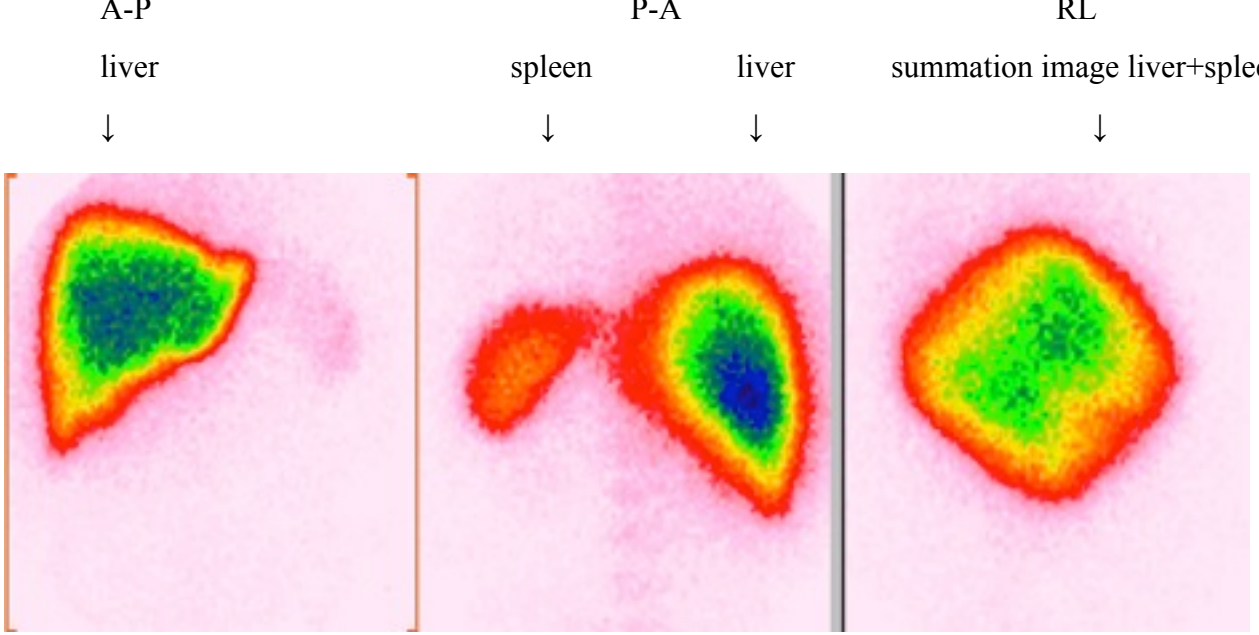


Fig III.4.2.1 planar - sodium phytate liver scintigraphy in A-P, P-A, RL projections.

Classical liver angioscintigraphy requires bolus intravenous injection of 260-370MBq (7-10mCi) ^{99m}Tc - sodium phytate, rapid, dynamic image acquisition initiated at the same time as the injection, at a rate of one image per second, for the duration of a minute. (Grigorescu M, 2009; Dragoteanu M, 2004)

The hepatic perfusion index is calculated considering that the arterial bolus reaches simultaneously the kidney and the liver, because of the very close emergence of the hepatic and renal arteries from the aorta. The tracer influx arriving through the hepatic artery can be seen in the arterial segment, while the additional influx from the portal vein is represented on the interval located immediately after the renal peak. (Fig.III.4.1.1). (Dragoteanu, 2004)

The normal values for this parameter are between 25-40%.

III.3 Transrectal portal scintigraphy

In order to establish the stage of chronic diffuse liver diseases, a method for assessing the shunts between the portal vein and the inferior vena cava has been developed.

The transrectal portal scintigraphy using ^{99m}Tc - pertechnetat was introduced to our laboratory by Prof. Cotul Sabin, PhD, in 1985.

Shiomi and colab. Described in 1988 two models, normal and pathological, of transrectal portal scintigraphy.

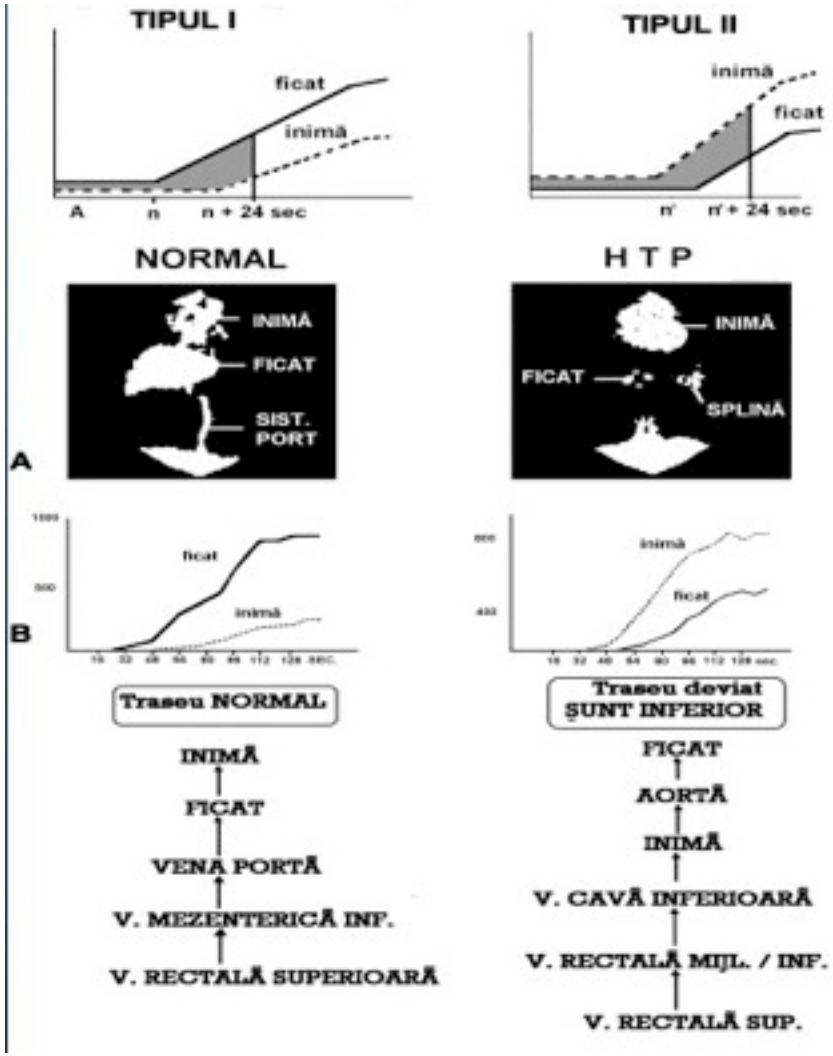


Fig.III.5.3
Type I – normal transrectal portal scintigraphy; n = the uptake of the radiotracer in the liver

Type II – pathological transrectal portal scintigraphy; n' = uptake of the radiotracer in the heart

(After Shiomi, 1988)

IV Non-conventional use of radiotracers in order to reinstate dynamic hepatobiliary scintigraphy (DHBS) and liver scintigraphy (LS)

IV.1 Practical justification of set objectives

Scintigraphy was in the 70s and 80s the standard imaging technique used for the morphological and functional assessment of the liver. (Cotul S, 1988)

Hepatic scintigraphy provides methods of differential investigation of the parenchyma, biliary ducts, mesenchyme, arterial and portal circulation.

The development of technology in the past few decades has lead to the emergence of new types of performant imaging techniques for the anatomical assessment of the liver: CT, MRI, PET SCAN, ultrasonography, all providing resolution superior to scintigraphy.

Nuclear medicine has, however, retained an important place within Medical imaging because of the functional and physiopathological assessments it provides and which are less available to the morphological investigations.

Dynamic hepatic scintigraphy brilliantly illustrates this point by providing a wealth of information found in the calculated parameters.

Hepatic angioscintigraphy and the hepatic perfusion index provide information on the proportion of portal and arterial circulation, respectively, within the liver.

The studies performed in our laboratory, some for the first time, revealed the possibilities of assessing portal hypertension and of discriminating by *IPH?* between malignant and benign tumors of the liver. (Dragoteanu M, 2004; Ioana G, 2008)

Hepatic scintigraphy with labeled autologous red blood cells preceded by radiocolloid scintigraphy is the only imaging technique ensuring the differential diagnosis of hepatic hemangiomas larger than 1,5 cm in diameter.

The results obtained over time have confirmed its position as the most precise method for establishing the hemangiomatous nature of a tumor described as lacunar by radiocolloid scintigraphy. (Cotul S, 1971; Grigorescu M, 2004)

Dynamic hepatobiliary scintigraphy explores the intra- and extrahepatic biliary ducts; the interpretation of dynamic curves is one of the best diagnostic methods for several conditions, such as: acute and chronic cholecystitis, biliary dyskinesia, gallbladder carcinoma, as well as for postoperative assessment of the biliary tract, detection of biliary leaks, monitoring of drainage through surgical anastomoses, etc. (Grigorescu M, 2004)

Calculating the parameters resulted from data acquisition by means of performant equipment, as well as the necessity to obtain medical interpretation for difficult dynamics, were the main factors that lead to a limitation of the number of medical units where these Nuclear medicine methods were readily available.

The laws in our country allow the acquisition of pharmaceuticals used in Nuclear medicine only by CNCAN authorized firms for the marketing of particular isotopes and require type approval for the internal market. The type approval involves payment of a significant tax, which determined the few firms supplying the Romanian market to abandon the pharmaceuticals in lower demand.

Of the products destined for ^{99m}Tc labeling, sodium phytate - required for radiocolloid hepatic scintigraphy and HIDA (derivative of iminodiacetic acid) - used in dynamic hepatobiliary scintigraphy, became unavailable.

The constant request for these types of investigations has, however, prompted me to study the pharmacokinetics, mechanisms of localization and dosimetry of available pharmaceuticals, even if destined for different types of scintigraphic examinations, in the desire to reintroduce them in current practice.

IV.2 Study of chemical composition, radiochemistry, dosimetry and pharmacokinetics of ^{99m}Tc - Tetrofosmin when used in DHBS

At the beginning of 2009, the Myoview pharmaceutical (active substance - Tetrofosmin) was supplied to our laboratory for myocardial perfusion scintigraphies.

The radiotracer is eliminated via hepatobiliary route and its uptake in the bowel makes such scintigraphies difficult to interpret.

The study of available literature on the attempts to increase hepatobiliary excretion of ^{99m}Tc - Tetrofosmin in order to obtain higher resolution images of the myocardium made me consider the possibility to use this radiopharmaceutical for dynamic hepatobiliary scintigraphy. (Boz A, 2003; Boz A, 2001; Cerng SC, 2006; Gruning T, 2006; Higley B, 1993; Hofman M, 2006; Lyngholm AM, 2008; Peace RA, 2005; van Dongen, 2000; Masatake H, 2008; Germano G, 1994)

The active substance in Myoview is sodium tetrofosmin

[6,9-bis(2-ethoxyethyl)-3,12-dioxa-6,9-diphosphatetradecane] in dosage of 0,23 mg/phial. (www.**gehealthcare.com**/caen/md/docs/**myoview**pieng.pdf.)

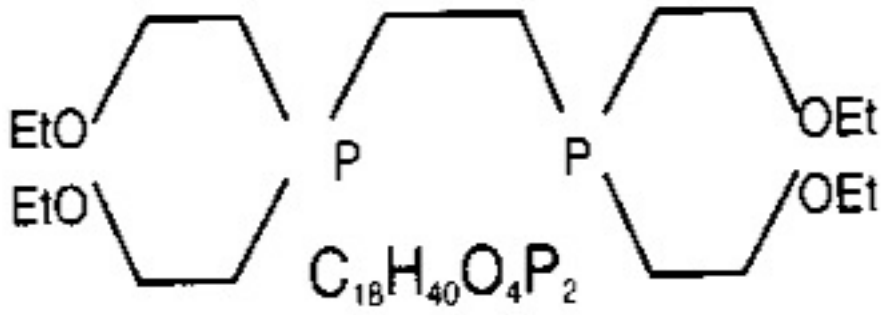


Fig . IV.2.1 Structural formula of tetrofosmin (Higley B., 1993)

Tetrofosmin is a polymer, similar to derivatives of iminodiacetic acid used usually in dynamic hepatobiliary scintigraphy, which are, from a chemical point of view, high molecular weight trimers (triligands).

More specifically, Tetrofosminul is a dimer with a molecular weight of 382, which after binding to ^{99m}Tc forms a molecular complex with a molecular weight of 895. (Guhlke S, 2007; Taillefer R, 2001)

The investigation we propose here requires 8-10 fold lower doses than in myocardial perfusion scintigraphies; this ensures a low enough level of internal irradiation (expressed as actual dose) to justify the use of ^{99m}Tc -Tetrofosmin dynamic hepatobiliary scintigraphy from the point of view of radioprotection, as well.

IV.3 Results and discussion

The physician in our department appreciated the scintigraphic images obtained with ^{99m}Tc -Tetrofosmin for the hepatobiliary dynamics as being of adequate quality for interpretation.

The visualization of the heart was not considered an impediment for the interpretation of hepatobiliary dynamics assessed using ^{99m}Tc -Tetrofosmin, nor did it require the use of higher doses than for the similar investigation using ^{99m}Tc -HIDA.

I presented further some of the conditions which documented the possibility to use ^{99m}Tc -Tetrofosmin for diagnostic hepatobiliary dynamic scintigraphy.

1. **Biliary dyskinesia –** gallbladder motility disorders due to lower ejection fraction or longer time of biliary evacuation in the intestine (Grigorescu M., 2004)

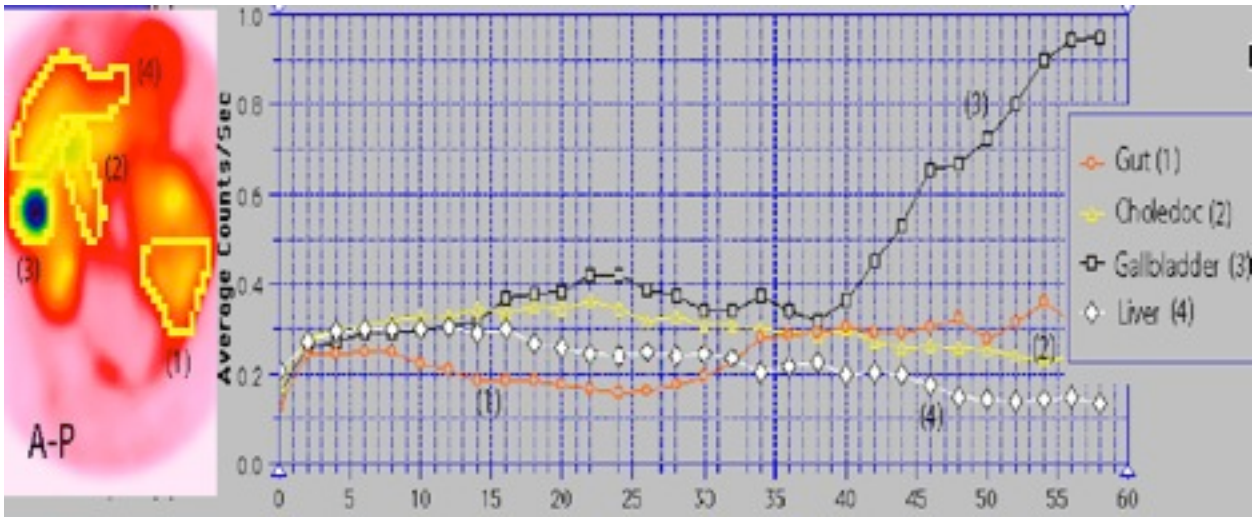


Fig. IV.2.4.1 Biliary dyskinezia manifested by lack of gallbladder emptying (3) 35 min after injection and by stasis in the choledocus (2) [Gut area (1), Liver (4)]

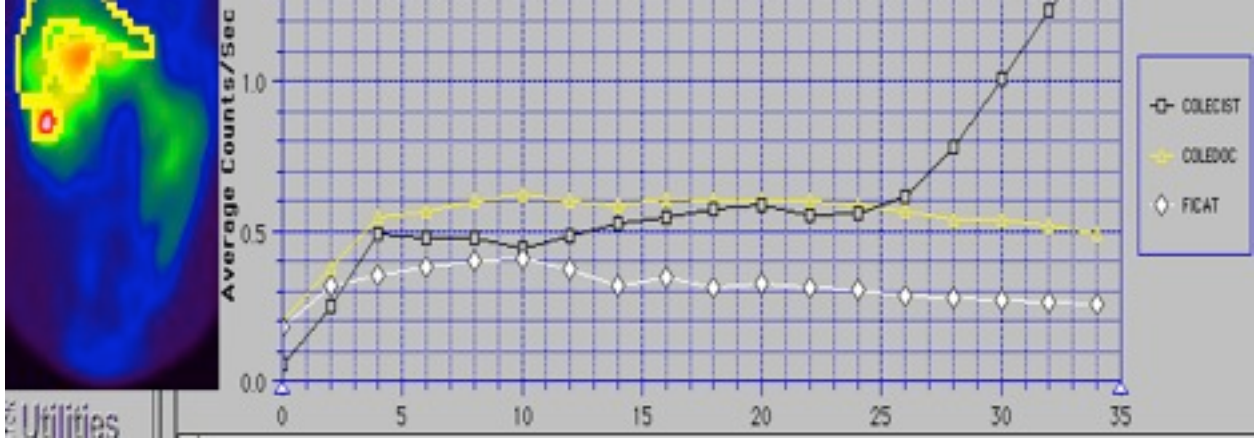


Fig. IV.2.4.2 Biliary dyskinezia manifested by lack of gallbladder emptying 35 minutes after injection.

The pharmacokinetics of the radiotracer proposed for dynamic hepatobiliary scintigraphy allow us to assess the late visualization of the gallbladder, even 2 and 3 hours after injection.

(Fig. IV.2.4.5 and Fig. IV.2.4.6)

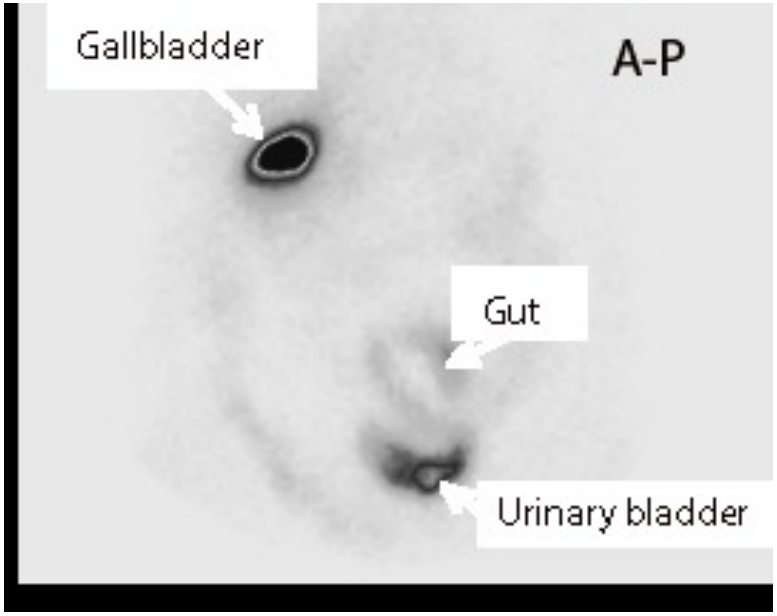


Fig. IV.2.4.5 Static scintigraphic image recorded 2 h after administration of the radiotracer with late visualization of the gallbladder and gut in a case of biliary dyskinesia.

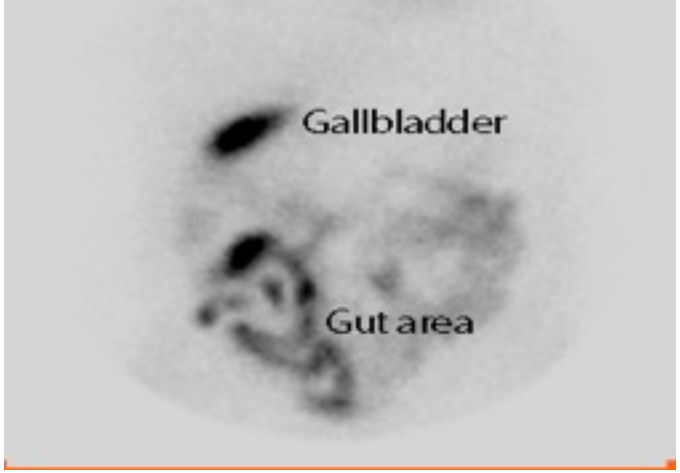


Fig. IV.2.4.6 Scintigraphic image recorded 3 hours after administration of radiotracer (the same as in the figure above) with late visualization of the gallbladder and gut area after eating a fat-rich meal.

2. **Transient intrahepatic stasis –** the evacuation of the radiopharmaceutical in the intrahepatic or extrahepatic bile ducts is delayed by an incomplete obstacle.

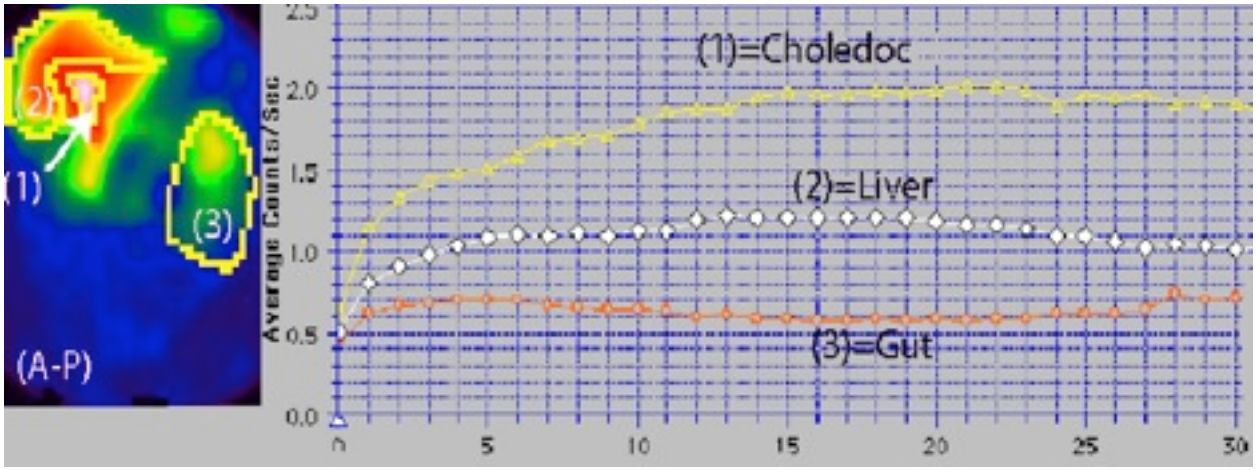
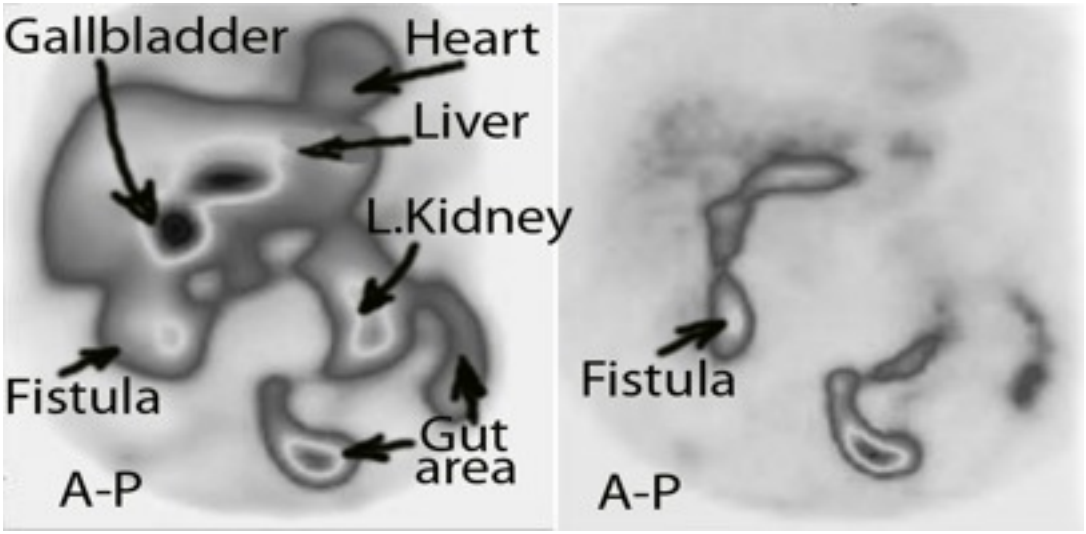


Fig. IV.2.4.7 Transient stasis in the choledocus (1) with delayed visualization of radiotraacer in the gut (3).

3. **Biliary fistulas –** either postoperative or posttraumatic, they can be visualized as abnormal radioactive structures that do not respect the biliary anatomy (Grigorescu M., 2004)

The quantity of radiotracer should be sufficiently large to properly view the biliary fistulas, because of their small dimensions.

We obtained sufficiently clear images of postoperative biliary enteric fistulas (Fig.IV.2.4.6) to confirm yet again the usefulness of ^{99m}Tc -Tetrofosmin for dynamic hepatobiliary scintigraphy.



I **II**

Fig.IV.2.4.9 Biliary enteric fistula:

I – static image of the abdominal area in A-P projection, obtained 1h after injection

II – static image in A-P projection obtained 2h after injection, with radiotracer visualized outside of the anatomical duct for gallbladder evacuation (fistula).

The scintigraphic visualization of the intrahepatic biliary tree, choledocus and gallbladder were appreciated as having sufficient resolution to be interpreted. It follows that the intra- and extrahepatic areas of stasis can be assessed when taking into consideration the pharmacokinetics of the tracer in these areas.

The amount of tracer evacuated through the bile is sufficient to allow the drawing of dynamic curves (number of impulses recorded on the interest area function of time) with good quantitative and temporal resolution. In addition, fine ducts become visible, such as biliary enteric or biliary bronchial fistulas.

The myocardial dynamics of ^{99m}Tc -Tetrofosmin allows an accurate late visualization of the biliary ducts through static images recorded up to 4 hours after injection. Using a similar dose to the one used in the ^{99m}Tc -HIDA investigation ensures the strict observance of the radioprotection rules with negligible irradiation of patient and staff.

Considering further the radioprotection norms, I consider that the objectives of the present study also comply with the ICRP appeal regarding the necessity to obtain the "maximum of information from any investigation involving radiopharmaceutical administration". This appeal was launched as early as 1971 by the Nuclear medicine community through the group for the protection of patients investigated using radiopharmaceuticals, and it was reiterated in 1988 in the IRCP 53 publication. (Sgouros S., 2009)

With ^{99m}Tc -Tetrofosmin being the first choice in performing perfusion myocardial scintigraphies (requiring 8-10 fold higher doses than hepatobiliary scintigraphy), using the residual tracer for dynamic hepatobiliary scintigraphy has its obvious economic advantages. Since the compound does not contain iodine, dynamic hepatobiliary scintigraphy using ^{99m}Tc -Tetrofosmin is feasible in allergic patients, where iodinated substances are contraindicated. The limitation of the method is the lack of stadialization of the times of activity apparition in the intra- and extrahepatic biliary duct and the gut, respectively.

IV.4 Using ^{99m}Tc - Nanocoll in hepatic scintigraphy

The only radiopharmaceutical available at present on the Romanian market is Nanocoll, produced by GE Healthcare. It has a colloidal form "in vitro", with colloidal particles the size of particles found in the liver macrophages (on the order of micrometers).

I studied the pharmacokinetics of this product in order to assess its potential use in classical hepatic scintigraphy (of any kind available in our laboratory: angioscintigraphy, planar hepatic scintigraphy and SPECT tomoscintigraphy), despite its original destination for lymphoscintigraphy (after subcutaneous injection), bone marrow scintigraphy (after intravenous injection), as well as for detection of inflammatory foci located outside the abdomen. The radiopharmaceutical is extracted from circulation after intravenous injection by the reticular

endothelial system in the liver, spleen and bone marrow, with only a small part eliminated in urine. A fraction of colloidal ^{99m}Tc - albumin was found in the liver even after subcutaneous administration.

IV.5 Results and discussion

We compared the quality of scintigraphic images obtained from scintigraphies performed with ^{99m}Tc - Nanocoll to those obtained with classical radiopharmaceutical, ^{99m}Tc - sodium phytate, from the data base of our laboratory. Upon medical interpretation, the ^{99m}Tc - Nanocoll hepatic scintigraphies were deemed comparable to the ^{99m}Tc - sodium phytate ones as far as quality was concerned, which meant that the newly-proposed method was able to successfully replace the classical one.

I present further some significant images for: hepatic angioscintigraphy, planar hepatic scintigraphies and tomoscintigraphies performed in our laboratory with the ^{99m}Tc - Nanocoll radiopharmaceutical. The proportion of radiotracer taken up by the hepatic Kupffer cells from the injected dose is sufficient to provide scintigraphic images of sufficient resolution for a good medical interpretation.

A-P (LIVER) P-A(Spleen+Liver)

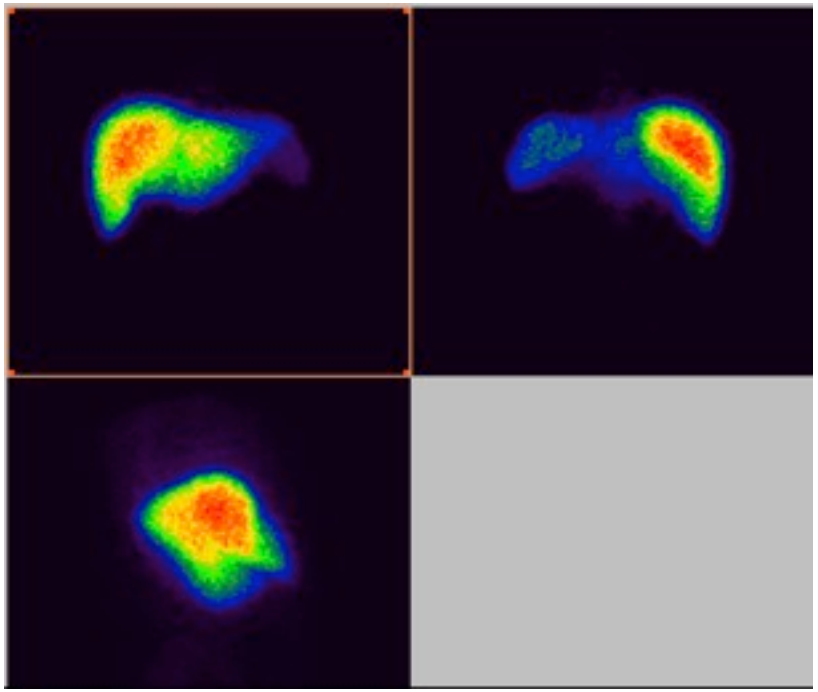
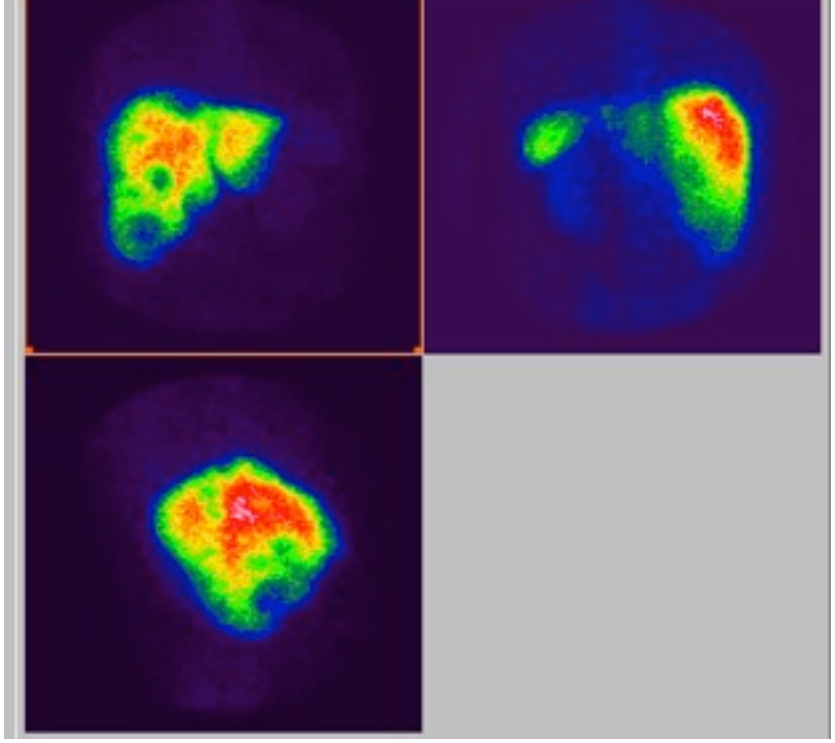


Fig.IV.3.4.3 Planar hepatic scintigraphy using ^{99m}Tc - Nanocoll 30 min after injection, in a normal subject, showing homogeneous fixation in the liver

Right lateral (summation image liver+spleen in right lateral projection)

A-P **P-A**



Right lateral

Fig. IV.3.4.5 Planar hepatic scintigraphy using **-** Nanocoll, 30 min after injection, in a patient diagnosed with liver metastases – circular areas with no tracer fixation well-visible in the hepatic area.

IV.4 Results and discussion

After intravenous injection, ^{99m}Tc **-** Nanocoll was found to be immediately extracted from circulation by the Kupffer cells, which lead to optimal visualization of the liver 15-30 minutes after injection.

The work protocol for every type of scintigraphy (planar, angioscintigraphy and tomoscintigraphy) implies the recording of angioscintigraphy first, at the same time as the bolus administration of the radiotracer (small volume dose: 0,2-0,3 ml), followed by planar scintigraphy 15-30 minutes later and in the end the recording of liver scintigraphy.

The prescribed dosage requires administration of a certain portion of the nanoparticles in a phial; we observed that using the entire quantity of ^{99m}Tc - Nanocoll leads to "too intense" images as compared with the background.

Recording the scintigraphic images involves a colour code (for coloured images) or a gray-scale with several shades for black-and-white images, with a certain number on impulses attributed to each colour or gray level.

The colour intensity is in direct proportion with the number of impulses emitted by the area exposed to the detector and with the area of highest activity.

A high number of nanoparticles present in the normal areas of the liver may "cover" the areas of hypofixation, which may impair the interpretation.

In order to improve the quality of scintigraphic images, we observed that a decrease of the quantity of nanoparticles in the phial is necessary before preparation. This was made possible by instilling a small volume of saline (approximately 1 ml) in the phial followed by removal of about a half of the contents.

The doses of radiopharmaceutical are prepared by adding sodium pertechnetate to the nanoparticles in the phial.

Controlling the human albumin nanoparticles in a dose improves significantly the sensibility of scintigraphic images.

The too intense images are explained for ^{99m}Tc - Nanocoll by the fact that the technetium binds to the nanoparticles in vitro and upon injection, almost all particles in the phial will already be bound to. **In contrast, when administering** ^{99m}Tc - sodium phytate, only a portion of it turns to radiocolloid after injection, in the presence of calcium ions in the blood.

A large number of nanoparticles are captured by the liver mesenchyme which translates as high activity in the normal hepatic areas, which can increase the activity in the adjoining areas of hypofixation, making them harder to spot on planar scintigraphy.

Increased activity at the periphery of hypofixating areas makes them appear smaller.

We have found that removing half of the nanocolloidal particles from the phial before technetium-labeling is a compulsory requirement to ensure high sensitivity images.

Performing three scintigraphic examinations with only one tracer injection is yet another motivation to continue performing hepatic scintigraphy with ^{99m}Tc - Nanocoll as well, both from a financial as from the point of view of radioprotection.

V. Observations on the dynamic curves obtained in transrectal portal scintigraphy and hepatic angioscintigraphy

This study aimed at explaining the rising dynamic curves obtained by transrectal portoscintigraphy (aspect due to radiotracer accumulation), while sodium pertechnetate is a radiotracer with no vascular or hepatic accumulation.

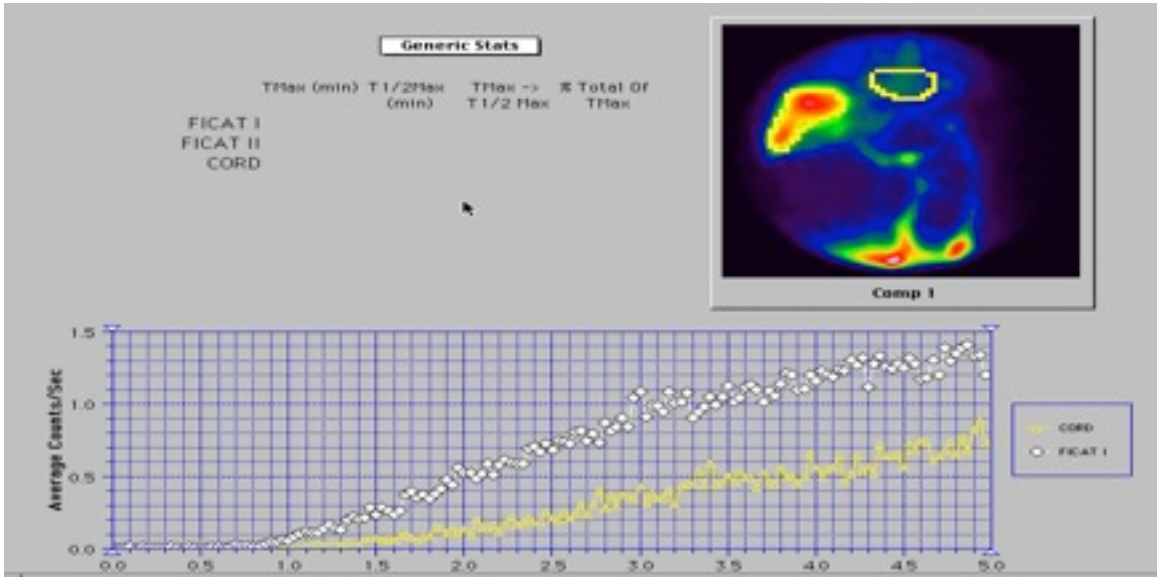


Fig. V.2.1.1 Transrectal portoscintigraphic curves in a normal subject; the liver curve precedes the cardiac one by 24s.

It is apparent that, starting from the point where the activity level is high enough to allow the recording of dynamic curves, these show an accumulation pattern until reaching a plateau.

The dynamic behaviour of the vascular radiotracer can therefore be interpreted only in the biophysical context of transrectal absorption.

The radiotracer, once absorbed, is continuously flushed by the blood from the superior rectal veins and then circulates through the entire organism.

The rectal absorption of pertechnetate requires a concentration gradient (which, according to definition, means a passive absorptive process).

Only the absorption through ionic channels or the facilitated diffusion could explain the shape of dynamic curves obtained from this examination.

On the other hand, the curve recorded on the inferior mesenteric vein also has an ascending slope. (Fig V.2.1.3).

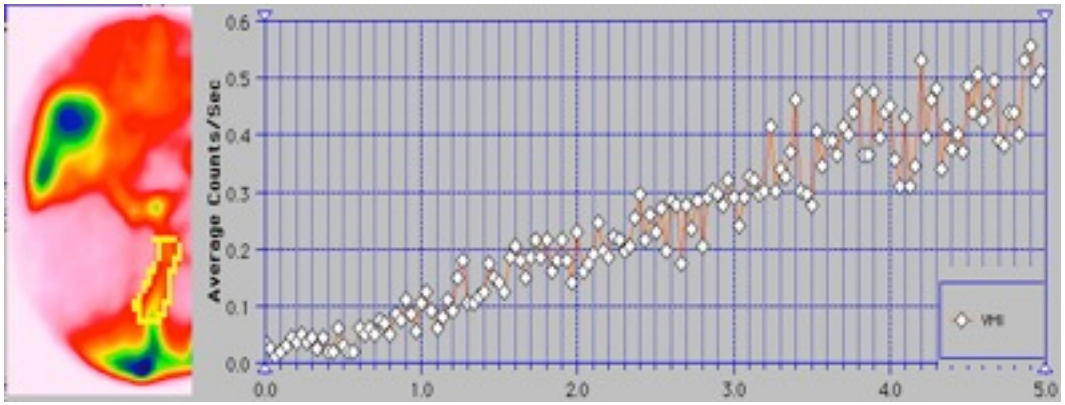


Fig V.2.1.3 Transrectal portoscintigraphic curve recorded on the inferior mesenteric vein (IMV)

Once in the liver of a normal subject, the radiotracer will remain there for 24 seconds.(Fig. V. 2.1.1)

The expected shape of the hepatic curve would result form the summation of tracer quantities reaching the liver through the IMV → integral of the function describing the IMV curve → it takes the shape of a parabola.

The recorded aspect does not correspond to expectations and was interpreted medically as a protection mechanism of the liver against double perfusion.

This mechanism is mirrored during hepatic angioscintigraphy with sodium pertechnetate; in this case, the tracer injected in bolus has the expected behaviour in the heart (uptake-release), while the curve recorded in the liver also has an ascending slope (although this tracer does not accumulate in the liver).

V.1 Study of the calculus formula for the shunt index computed on normal cases investigated with transrectal portal scintigraphy

d at transrectal

C).

$$(I)\quad ISPC = \frac{C_A(t_{0+24s})}{C_A(t_{0+24s}) + F_A(t_{0+24s})} \times 100\ (\%)$$

$$(II)\quad ISPC = \frac{C_A(t_{0'+24s})}{C_A(t_{0'+24s}) + F_A(t_{0'+24s})} \times 100\ (\%)$$

The two formulas correspond to the two possible situations: normal (I) and pathological (II) (Shiomi S., 1988)

C_A - area under the cardiac curve

F_A - area under the hepatic curve

t_0 - the moment the tracer is visualized in the liver (for formula I)

$t_o^{'}$ – the moment the tracer is visualized in the heart (for formula II)

24 s – mean time (expressed in seconds) spent in going through the liver and heart, as recorded in healthy patients.

The team I was a part of proposed that the first formula for ISPC as proposed by Shiomi&colab be modified so as to consider the areas delimited by the dynamic curves with the same dynamic behaviour of the radiotracer.

Therefore, we propose that only the area under the hepatic curve corresponding to the last 6 sec (for calculating the ISPC in our laboratory) be considered, since this last interval could be approximated in dynamic behaviour to that of the heart.

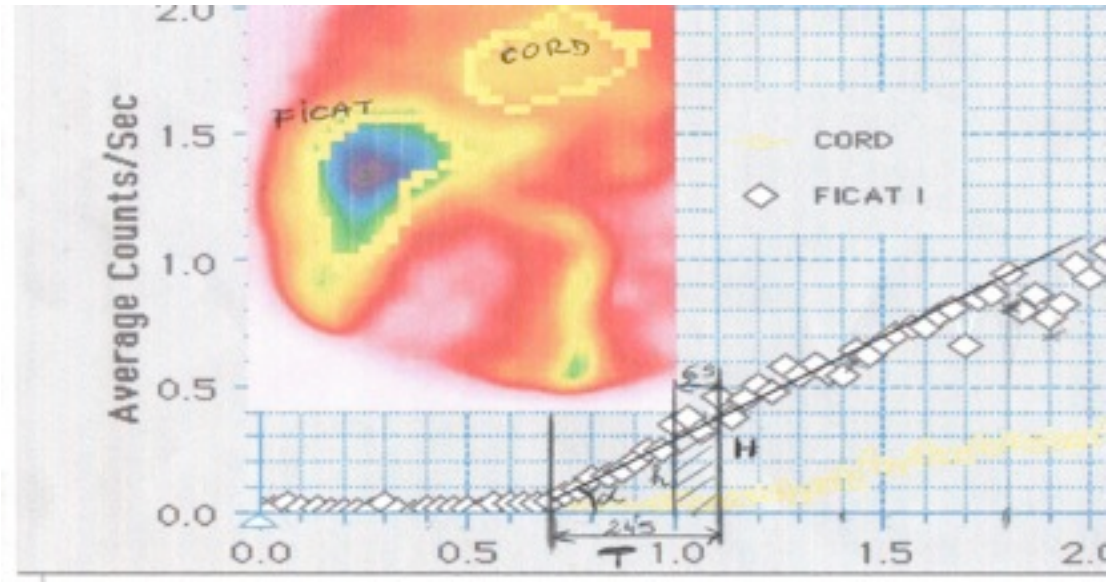


Fig.V.3.2 Graphic representation of the two curves (hepatic and cardiac); we highlighted the area under the hepatic curve to be compared to the area under the cardiac curve.

H – height of the hepatic curve at the point t_0 + 24s

T – considered time interval

α – value of the angle between the hepatic curve and the abscissa

h – height of the hepatic curve at the beginning of the last 6 second interval

Hatched area – area under the hepatic curve with a similar behaviour of the tracer as in the heart.

Under these circumstances, a new value of the portocaval shunt index results, noted from now on as $ISPC_{\sim F}$.

It follows that:

$ISPC_{\sim F} = \frac{16ISPC}{9ISPC + 7}$, a portocaval shunt index with slightly higher values than the one computed by Shiomi&colab, but considered correct by our team in view of the physiologic behaviour of the radiotracer.

VI. Final conclusions

1 Non-conventional use of certain radiotracers

1. **Performing dynamic hepatobiliary scintigraphy using ^{99m}Tc -Tetrofosmin, a radiopharmaceutical** designed for perfusion myocardial scintigraphy, is available for the diagnosis of biliary dyskinesia, stasis in the extra- and intrahepatic biliary ducts and biliary fistulas.

The administration of 8-10 times smaller doses than in myocardial perfusion scintigraphy recommends this investigation from the point of view of radioprotection, as well.

2. **Performing hepatic scintigraphy using ^{99m}Tc -Nanocoll,** radiopharmaceutical destined for lymphoscintigraphy and bone marrow scintigraphy, is possible and allows the scintigraphic assessment of the same conditions previously assessed using ^{99m}Tc -sodium phytate.

The resolution of scintigraphic images obtained with the proposed radiotracer can be improved by decreasing the number of nanoparticles (up to approximatively 1/3 of those existing in a phial) for the preparation of the radiopharmaceutical.

I have come across studies in literature on the scintigraphic assessment of liver transplant recipients using ^{99m}Tc -Nanocoll. My proposal regarding this investigation was to perform all three types of examinations: angioscintigraphy, planar hepatic scintigraphy and tomoscintigraphy after only one injection.

Such a procedure would limit the internal irradiation for the pacient, with good economical outcome, with only one tracer administration for three types of scintigraphy.

VI.2 Issues on the biophysics and dynamics of the radiotracer in transrectal portal scintigraphy

VI.2.1 Interpretation of the dynamic curves recorded in transrectal portal scintigraphy

The shape of the curves in transrectal portal scintigraphy can be interpreted only when studying the type of transmembrane transport of ^{99m}Tc -sodium pertechnetate.

The initial aspect (the first 1-3 minutes) of the ascending slope can only be explained by a mechanism implying an increasing velocity characteristic to the ionic channel transport or to facilitated diffusion taking place during that interval.

The dynamic curves having an ascending slope recorded during both transrectal portal scintigraphy and hepatic angioscintigraphy using sodium pertechnetate, when it is known that this tracer does not fixate in the liver, illustrates the way the liver protects itself against double perfusion, arterial and venous.

VI.2.2 Observations on the calculus of the portocaval shunt index during transrectal portal scintigraphy

Regarding the first formula for the calculation of ISPC, issued by Shiomi&colab. (Shiomi S., 1988), our team proposed to consider the physiological behavior of the radiotracer when passing through the liver and to correlate it with its behavior in the liver.

We found therefore a portocaval shunt index of slightly higher values than the ones obtained by Shiomi&colab.

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