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Article

# Hepatic and Pulmonary Vasoactive Response Triggered by Potentially Hazardous Chemicals After Passing Through the Gut Mucosa

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## Abstract

**Background/Objectives:** In a previous study, we observed significantly prolonged hepatic and pulmonary first-pass transit times (TTs) for <sup>99m</sup>Tc-pertechnetate absorbed through the colorectal mucosa during per-rectal portal scintigraphy (PRPS). These effects were not observed when <sup>99m</sup>Tc-pertechnetate was administered into the spleen during trans-splenic portal scintigraphy or injected intravenously in radionuclide angiocardiology. We hypothesized that <sup>99m</sup>Tc-pertechnetate is recognized in the colorectal mucosa as a potentially hazardous chemical (PHC), with its transhepatic and transpulmonary slowdown aiding in its removal. A similar reduction in portal flow, triggered by vasoactive circulating mediators, occurs during early metastasis of colorectal cancer (CRC), as indicated by a pathological increase in the hepatic perfusion index calculated using liver angioscintigraphy (LAS). We aimed to examine the hepatic and pulmonary vasoactive response triggered by PHCs after they pass through the gut mucosa and assess their pathological activation in early CRC metastasis. **Methods:** We measured TTs to determine whether hepatic and pulmonary vasoconstriction occurs in response to radiotracers administered at different sites. PRPS using <sup>99m</sup>Tc-pertechnetate evaluated the liver transit time (LTT) and right heart-to-liver circulation time (RHLT) of the colorectal-absorbed <sup>99m</sup>Tc-pertechnetate. LAS assessed RHLT and LTT following the intravenous injection of radiotracers based on <sup>99m</sup>Tc. Lower rectum transmucosal dynamic scintigraphy (LR-TMDS) measured RHLT of <sup>99m</sup>Tc-pertechnetate delivered into the lower rectum submucosa. LTT and RHLT were compared to similar TTs observed by other imaging methods. **Results:** In healthy volunteers, PRPS showed notably longer LTT (average: 24 s) and RHLT (average: 42 s) for colorectal-absorbed <sup>99m</sup>Tc-pertechnetate. Significantly lower RHLT values (9–13.5 s) were observed for <sup>99m</sup>Tc-pertechnetate and <sup>99m</sup>Tc-HDP (hydroxyethylene-diphosphate) administered intravenously during LAS, as well as for <sup>99m</sup>Tc-pertechnetate injected into the submucosa at LR-TMDS (12–15 s). The LTT assessed at LAS for <sup>99m</sup>Tc-HDP given intravenously ranged from 22 to 27 s, consistent with the range seen at PRPS for <sup>99m</sup>Tc-pertechnetate after colorectal absorption. **Conclusions:** An intense vasoconstriction happens in the liver and lungs when foreign substances, recognized by the body as PHCs, pass through the gut mucosa, helping their elimination.

**Keywords:** vasoconstriction; portal flow; pulmonary blood flow; per-rectal portal scintigraphy; liver angioscintigraphy; colorectal cancer; early metastasis

## Introduction

$^{99m}\text{Tc}$ -pertechnetate absorbed from the upper rectum and terminal colon in per-rectal portal scintigraphy (PRPS) shows a three- to fourfold increase in the liver transit time from the portal vein to the right atrium (LTT), and in the circulation time from the right heart (more precisely – the right atrium) to the liver (RHLT) - which mainly includes the transpulmonary transit time [1]. In contrast, a prolonged LTT was not observed for  $^{99m}\text{Tc}$ -pertechnetate administered into the spleen during trans-splenic portal scintigraphy (TSPS) [2,3], and transpulmonary transit time was not increased for  $^{99m}\text{Tc}$ -pertechnetate given intravenously in radionuclide angiocardiology [4]. This indicates that the absorption of  $^{99m}\text{Tc}$ -pertechnetate in the colorectum is essential for slowing the radiotracer flow through the liver and lungs, as noted in PRPS. Since  $^{99m}\text{Tc}$ -pertechnetate is an artificially produced substance, we hypothesize that the reduced hepatic and pulmonary transit rates of colorectal-absorbed  $^{99m}\text{Tc}$ -pertechnetate may result from an unidentified defense mechanism activated against unknown substances absorbed from the gut, which the body recognizes as potentially hazardous chemicals (PHCs). The low LTTs of the radiotracers injected into the spleen during TSPS suggest that  $^{99m}\text{Tc}$ -pertechnetate cannot directly trigger first-pass vasoconstriction in the liver. The normal range observed for transpulmonary transit time of  $^{99m}\text{Tc}$ -pertechnetate administered intravenously during radionuclide angiocardiology indicates that  $^{99m}\text{Tc}$ -pertechnetate cannot directly cause first-pass vasoconstriction in the lungs. Therefore, other substances are responsible for triggering the hepatic and pulmonary vasoconstriction during PRPS. Therefore, we hypothesize that vasoactive agents (VAs) released from the colorectal wall during the absorption of  $^{99m}\text{Tc}$ -pertechnetate are the direct cause of the hepatic and pulmonary vasoconstriction observed in PRPS. This protective physiological response must target PHCs, which are accidentally ingested with food. It also suggests that this response can be triggered by certain medications or synthetic food additives taken orally.

A sudden decrease in portal flow, similar to that observed with  $^{99m}\text{Tc}$ -pertechnetate in PRPS, has been reported during the early stages of liver metastasis in colorectal cancer (CRC), but not in cancers outside the intestine [5,6,7]. The activation of this vasoactive mechanism, which is specific to CRC, appears to be closely linked to substances released from the colorectal wall, much like the anti-PHC response triggered at PRPS against  $^{99m}\text{Tc}$ -pertechnetate.

Our study was designed to examine the first-pass vasoactive response to  $^{99m}\text{Tc}$ -pertechnetate in the liver and lungs, as observed at PRPS. Using the dynamic data from time-activity curves generated at LAS, we also aimed to determine whether a radiotracer reaching the digestive tract mucosa via arterial flow can initiate the anti-PHC response in the liver.

This study could be beneficial for pharmacokinetics, toxicology, and the food industry, and it may also have implications for oncology, especially in CRC. Identifying the VAs can help in early diagnosis and targeted treatment of CRCs in patients at high risk of metastasis [5,8]. Targeting either the VAs or their receptors with specific medications may slow down or prevent the spread of CRC to the liver and potentially to the lungs, thereby increasing life expectancy for patients with this disease.

## Materials and Methods

### *Patient Population:*

All patients and healthy volunteers provided informed consent before participation, and the confidentiality of their data was maintained throughout the study. The hospital's ethics committee approved the nuclear medicine procedures and the scientific use of the laboratory database. The procedures involved subjects aged 18 to 85 who were required to fast for 12 hours prior to participation. We applied the following exclusion criteria, focusing on conditions that could affect blood flow transit times (TTs) through the liver and lungs: a) Patients diagnosed with heart failure, intracardiac or portosystemic shunts, or pulmonary illnesses were excluded from the RHLT

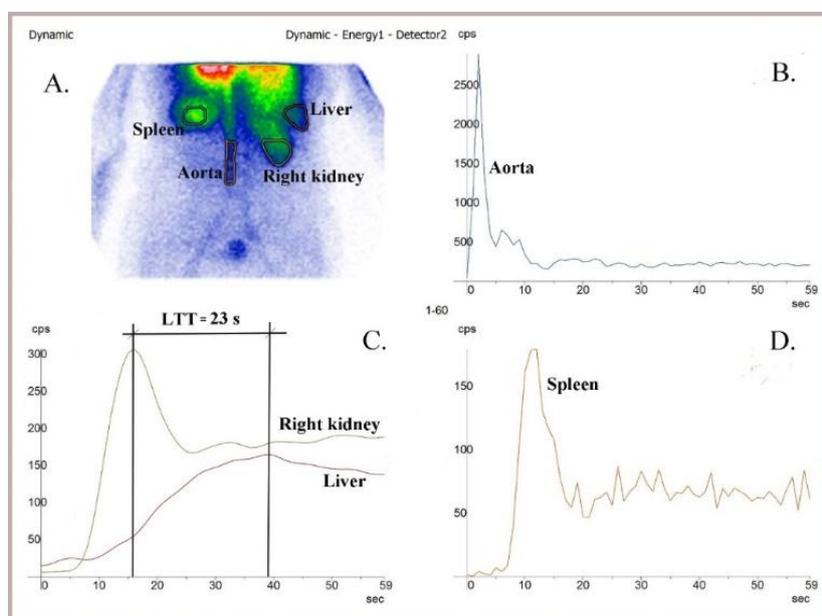
calculation. b) Patients diagnosed with diffuse liver disease, hemangiomas larger than 4 cm in diameter, or portosystemic shunts were excluded from the LTT calculation; c) Patients with hyperthyroidism were excluded from the RHLT calculation in LAS with  $^{99m}\text{Tc}$ -pertechnetate. d) Subjects who received unsuccessful bolus injections at LAS were also excluded; e) Additionally, we removed cases where time-activity curves showed low resolution or where the difference between the TTs evaluated by two experienced observers exceeded 15%.

The LAS studies involved patients referred for thyroid or skeletal scans who received the standard dose of radiotracer given as a bolus. This selection enabled RHLT and LTT assessment without unnecessary radiation exposure.

### Imaging Studies

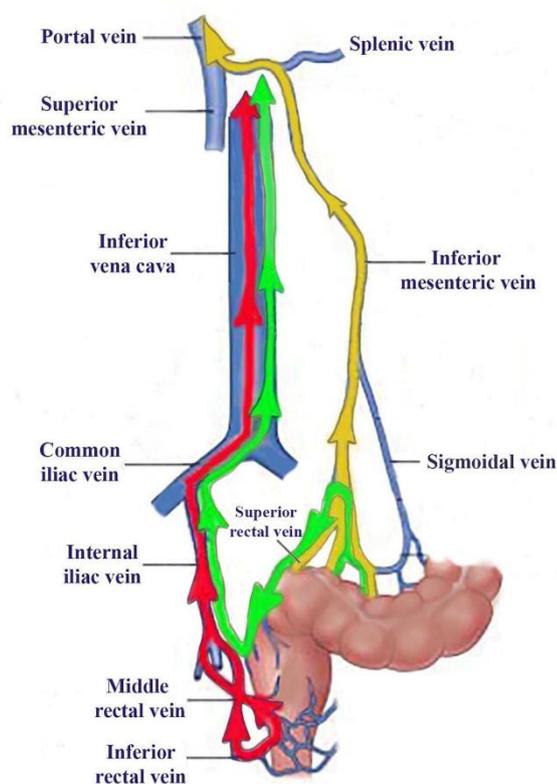
a) In previous studies, we performed PRPS using the methodology developed by Shiomi et al. [6]. We introduced two new parameters, LTT and RHLT, to assess the transit of  $^{99m}\text{Tc}$ -pertechnetate through the liver and lungs following colorectal absorption.

b) We used the methodology proposed by Leveson and Sarper to perform LAS [9,10]. After the intravenous antecubital bolus administration of the radiotracer, we recorded serial anteroposterior and posteroanterior images of the chest and upper abdomen every second for one minute. The bolus quality was verified by measuring the time from the half-maximum value to the peak of the renal curve, which must be under 8 s [11]. To assess RHLT for  $^{99m}\text{Tc}$ -pertechnetate, seven females and three males aged 29 to 64, who were referred for thyroid scans, underwent LAS with a dose of 150 to 185 MBq. To evaluate RHLT for  $^{99m}\text{Tc}$ -HDP (hydroxyethylene diphosphate), we performed LAS (Figure 1) with a dose of 300–370 MBq, in six healthy volunteers (four males and two females, aged 35–62 years) and in 43 patients referred for bone scans. Eleven patients were excluded due to low-resolution dynamic curves or incorrect bolus administration, resulting in a final analysis cohort of six controls and 32 patients: 18 males and 14 females, with ages ranging from 44 to 83 years and 33 to 72 years, respectively.



**Figure 1.** Liver angioscintigraphy performed using  $^{99m}\text{Tc}$ -HDP in a healthy patient. (A) Summed image. (B) Control of bolus quality on the dynamic curve built on the aorta. (C) The determined LTT was 23 s. (D) Dynamic comparative curve built on the spleen. The hepatic perfusion index was within the normal range (HPI = 30%). The study was conducted using an AnyScanS gamma camera (Mediso, Budapest, Hungary) in the posteroanterior (P-A) view.

c) We introduced lower rectum transmucosal dynamic scintigraphy (LR-TMDS) as a variant of PRPS to evaluate the RHLT of  $^{99m}\text{Tc}$ -pertechnetate injected into the submucosa of the lower rectum. Before reaching the right atrium, the radiotracer sequentially passed through the inferior rectal veins, the internal and common iliac veins, and the inferior vena cava. This pathway resembled that observed in patients with complete portal vein occlusion, as examined in PRPS, but did not involve the absorption of  $^{99m}\text{Tc}$ -pertechnetate through the colorectal mucosa (Figure 2). LR-TMDS was performed on four volunteers without any pathology of the lower rectum: one female and three males, aged 41 to 58 years. We injected a dose of 150–160 MBq of  $^{99m}\text{Tc}$ -pertechnetate into the lower rectum submucosa using a proctoscope positioned 5 to 8 cm from the anus. We then captured serial anteroposterior and posteroanterior images of the chest and upper abdomen at two-second intervals for four minutes. RHLT was calculated using time-activity curves made for the right heart and left kidney regions. We focused on the start of the time-activity curve of the left kidney, as the radiotracer reached the kidneys and liver simultaneously; however, the onset of the hepatic curve was less clear.



**Figure 2.** The vascular pathways of  $^{99m}\text{Tc}$ -pertechnetate during our investigations: absorbed in PRPS in patients with complete portal vein obstruction (green) and healthy volunteers (yellow), as well as after LR-TMDS administration into the submucosa of the lower rectum (red). The RHLT for  $^{99m}\text{Tc}$ -pertechnetate was 41–43 s in cases of portal vein obstructions explored at PRPS and only 12–15 s at LR-TMDS. For  $^{99m}\text{Tc}$ -pertechnetate delivered to the liver via the portal vein, following colorectal absorption in healthy volunteers at PRPS, the mean LTT was 24 s, and the mean RHLT was 42 s.

d) We assessed LTT using LAS to determine whether the radiotracer's flow through the liver slows down when  $^{99m}\text{Tc}$ -HDP is injected intravenously and reaches the portal circulation after passing through the mesenteric arteries and gut mucosa. LTT was measured in five healthy volunteers (three males and two females, aged 40 to 61 years) and 61 patients referred for a bone scan with  $^{99m}\text{Tc}$ -HDP. We used a technique similar to that employed for RHLT measurement at LAS, while recording anteroposterior and posteroanterior images of the abdomen. The peak of the left kidney's time-activity curve was used to determine when the portal flow of the radiotracer entered the liver. The peak of the liver's time-activity curve indicated when the radiotracer's portal flow exited the liver. In

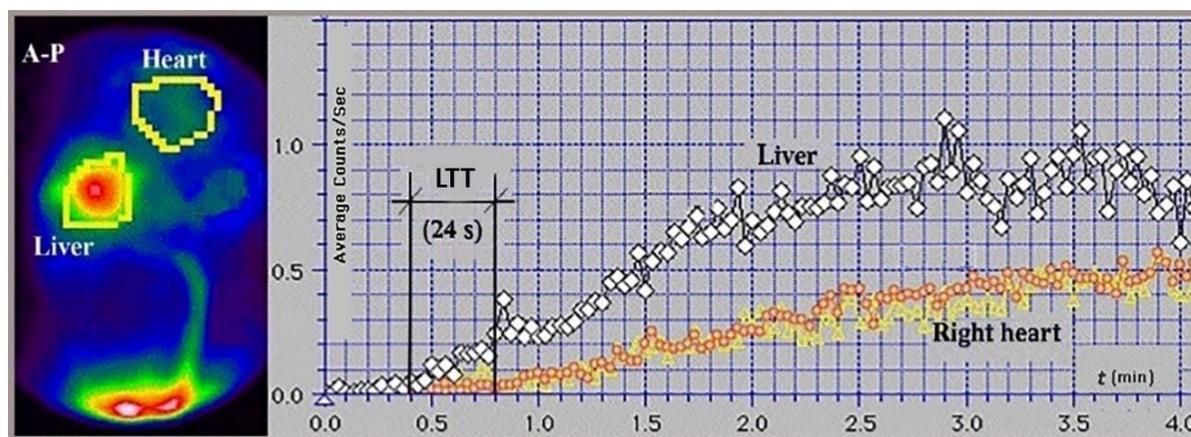
five healthy subjects and forty patients (15 women, aged 33 to 70 years, and 25 men, aged 42 to 82 years), the peak of the hepatic curve was visible, allowing LTT to be measured. The remaining participants were excluded from the study.

We conducted LAS and LR-TMDS studies using an AnyScanS gamma camera (Mediso, Budapest, Hungary) equipped with a high-resolution, low-energy parallel collimator, as well as Nucline v2.02 and InterView-XP dedicated software. Patients were positioned in a supine posture.

## Results

### 1.1. LTT and RHLT Determined in PRPS Performed with $^{99m}\text{Tc}$ -Pertechnetate

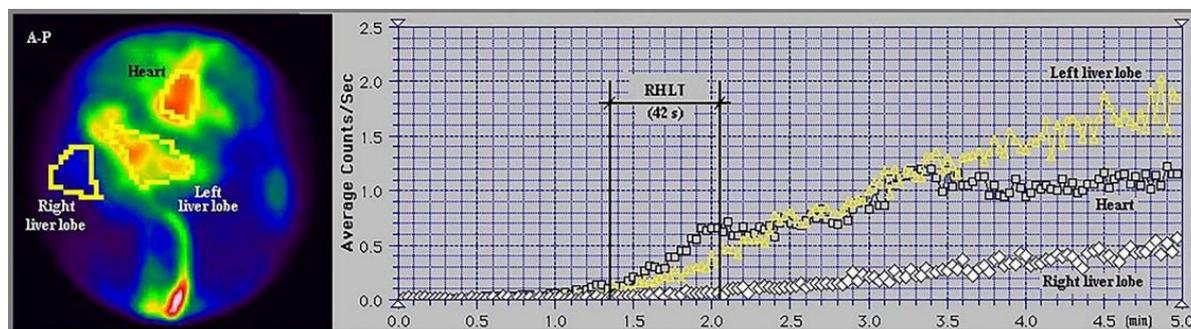
In a previous PRPS study using  $^{99m}\text{Tc}$ -pertechnetate, the LTT was  $24 \pm 1$  s in healthy volunteers (Figure 3).



**Figure 3.** Summed image and time-activity curves generated for the liver and heart regions during per-rectal portal scintigraphy using  $^{99m}\text{Tc}$ -pertechnetate in a healthy volunteer. The liver transit time from the portal vein to the right atrium (LTT) was 24 s. The study was performed using an Orbiter SPECT gamma camera (Siemens, Erlangen, Germany) in an anteroposterior (A-P) view.

Patients with diffuse liver disease showed LTT changes that correlated with the type and stage of the illness, reflecting alterations in the resistance the liver provides to portal inflow.

The mean RHLT was 42 s (Figure 4) and exhibited a slight variation of  $\pm 5\%$ , regardless of the presence or stage of liver disease [1].



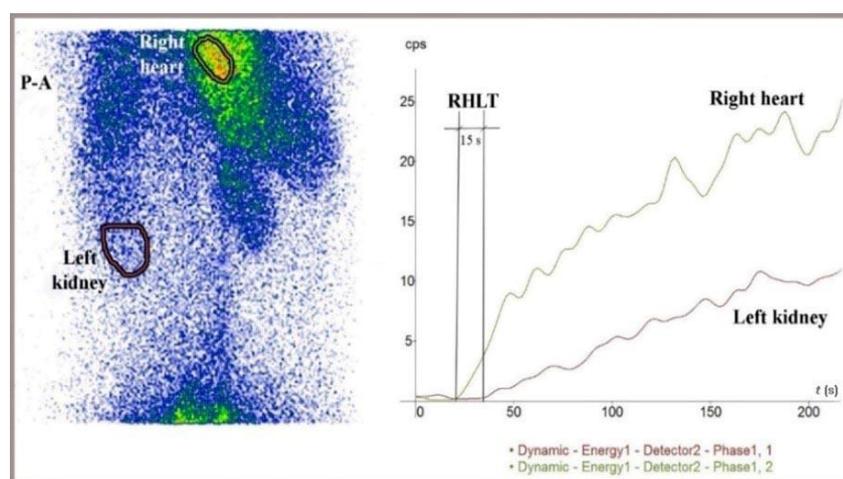
**Figure 4.** Summed image and time-activity curves generated in per-rectal portal scintigraphy performed with  $^{99m}\text{Tc}$ -pertechnetate in a patient with alcoholic cirrhosis and complete occlusion of the right portal vein branch. The right heart-to-liver circulation time (RHLT) determined for the right liver, which completely lacked portal inflow, was 42 s. This study used a Siemens Orbiter SPECT gamma camera in an anteroposterior (A-P) view.

### 1.1. RHLT Determined in LAS Performed with $^{99m}\text{Tc}$ -Pertechnetate and $^{99m}\text{Tc}$ -HDP

RHLT measured in LAS ranged from 9 to 13 s using  $^{99m}\text{Tc}$ -pertechnetate and from 9.5 to 13.5 s using  $^{99m}\text{Tc}$ -HDP. These values were approximately four times lower than those determined in PRPS, indicating that the intravenously injected  $^{99m}\text{Tc}$ -pertechnetate and  $^{99m}\text{Tc}$ -HDP did not slow down during their first pass through the lungs ( $P < 0.001$ ). This result shows that the radiotracers based on  $^{99m}\text{Tc}$  we used, do not directly cause vasoconstriction in the lungs.

### 1.1. RHLT Evaluated for $^{99m}\text{Tc}$ -Pertechnetate in LR-TMDS

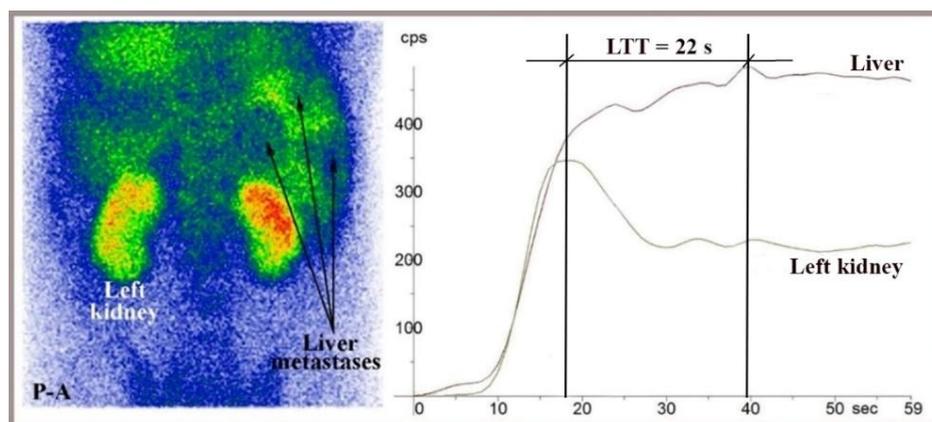
RHLT measured in LR-TMDS (Figure 5) for  $^{99m}\text{Tc}$ -pertechnetate injected into the lower rectum submucosa ranged from 12 to 15 s.  $^{99m}\text{Tc}$ -pertechnetate reached the right atrium by passing through the inferior hemorrhoidal veins, iliac internal and common veins, and vena cava in sequence. This pathway resembled that of  $^{99m}\text{Tc}$ -pertechnetate in PRPS performed in patients with complete portal vein occlusion, resulting in a significantly longer RHLT of  $42 \pm 1$  s.



**Figure 5.** Summed image and time-activity curves generated for the left kidney and right heart during lower rectum transmucosal dynamic scintigraphy (LR-TMDS) following the administration of  $^{99m}\text{Tc}$ -pertechnetate into the submucosa of the lower rectum. The right heart-to-liver circulation time (RHLT) was 15 s. We used the dynamic curve of the left kidney because the radiotracer reaches the liver and kidneys simultaneously, but the liver curve's onset is less clear. The study was performed using a Mediso AmyScanS gamma camera in a posteroanterior (P-A) view.

### 1.1. Assessment of LTT by Analyzing Time-Activity Curves Built at LAS

The time-activity curves created at LAS help us determine when the radiotracer delivered through portal inflow reaches the liver (matching the peak of the left or right kidney dynamic curve) and when the portal inflow of radiotracer then begins to leave the liver (indicated by the peak of the dynamic curve on the liver). LTT is the time between these two points (**Figure 1** and **Figure 6**). We used time-activity curves based on the spleen and aorta to verify the accurate delivery of the radiotracer bolus. LTT values measured at LAS for  $^{99m}\text{Tc}$ -HDP, delivered to the gut mucosa via arterial flow after intravenous injection, ranged from 20 to 27 seconds, aligning with the 24-second mean value recorded at PRPS for colorectal-absorbed  $^{99m}\text{Tc}$ -pertechnetate. LTT measured at LAS remained within this range even for patients with overt liver metastases from various cancers who did not have a portosystemic shunt (Figure 6).



**Figure 6.** Liver angioscintigraphy performed with  $^{99m}\text{Tc}$ -HDP on a 44-year-old patient showing overt liver metastases from CRC, visible on the summed image. LTT calculated from the dynamic curves was 22 seconds. The hepatic perfusion index was markedly increased at 87.5%. This study was carried out using a Mediso AmyScanS gamma camera with a posteroanterior (P-A) view.

### 1.1. Significance of the Results

No correlation was found between the TTs we evaluated and sex or age. Table 1 summarizes the studies conducted, the main findings, and their significance.

**Table 1.** Significance of the results of the dynamic nuclear medicine investigations conducted in the study. PRPS: per-rectal portal scintigraphy; LTT: liver transit time, from the portal vein to the right atrium; RHLT: the right heart to liver circulation time; LAS: liver angioscintigraphy; PHC: potentially hazardous chemical; LR-TMDS: lower rectum transmucosal dynamic scintigraphy; HDP: hydroxyethylene diphosphate.

Sr. No.	Imaging method	The transit time value determined	Significance of the results
1.	PRPS with $^{99m}\text{Tc}$ -pertechnetate (performed in a previous study)	Highly increased LTT (mean: 24 s) and RHLT (mean: 42 s)	First-pass vasoconstriction is triggered in the liver and lungs in response to colorectal-absorbed $^{99m}\text{Tc}$ -pertechnetate, recognized by the body as a PHC.
2.	LAS conducted to evaluate RHLT for intravenously injected $^{99m}\text{Tc}$ -HDP	Low value of RHLT (9.5-13.5 s)	$^{99m}\text{Tc}$ -HDP, when administered intravenously, cannot directly trigger first-pass vasoconstriction in the lungs.
3.	LAS conducted to evaluate RHLT for intravenously injected $^{99m}\text{Tc}$ -pertechnetate	Low value of RHLT (9-13 s)	$^{99m}\text{Tc}$ -pertechnetate, when injected intravenously, cannot directly trigger first-pass vasoconstriction in the lungs.

4.	LR-TMDS conducted to evaluate RHLT for $^{99m}\text{Tc}$ -pertechnetate administered in the lower rectum submucosa	Low value of RHLT (12-15 s)	Even if $^{99m}\text{Tc}$ -pertechnetate crosses the other layers of the colorectal wall but is not absorbed through the mucosa, it cannot directly activate first-pass vasoconstriction in the lungs. This indicates that the vasoactive agents that trigger vasoconstriction in PRPS are secreted in the colorectal mucosa.
5.	LAS conducted to evaluate LTT for intravenously injected $^{99m}\text{Tc}$ -HDP	Highly increased LTT (20-27 s)	Vasoconstriction is activated in the liver in response to $^{99m}\text{Tc}$ -HDP, which is delivered to the gut mucosa through arterial flow after intravenous injection.

## Discussion

### 1.1. Activation of the First-Pass Vasoactive Response in the Liver and Lungs to Facilitate the Removal of PHCs Absorbed from the Gut

In PRPS using  $^{99m}\text{Tc}$ -pertechnetate, the mean value determined for LTT in healthy individuals was significantly higher than those observed in TSPS [2,3,12], MRI [13], and contrast-enhanced ultrasound [14,15,16,17]. The RHLT measured at PRPS using  $^{99m}\text{Tc}$ -pertechnetate was approximately 42 s, which is significantly higher than in LR-TMDS, LAS, and the right atrium to left ventricle transit time measured during radionuclide angiography [4] (see Table 2).

**Table 2.** Mean values of LTT, right atrium to left ventricle transit time, and RHLT were measured in healthy controls using various imaging methods. LTT: liver transit time, from the portal vein to the right atrium; RHLT: the right heart to liver circulation time; PRPS: per-rectal portal scintigraphy; MRI: magnetic resonance imaging; PHC: potentially hazardous chemical; TSPS: trans-splenic portal scintigraphy; LAS: liver angioscintigraphy; LR-TMDS: lower rectum transmucosal dynamic scintigraphy.

Sr. No.	Imaging method	LTT	The transit time between the right atrium and the left ventricle	RHLT
1.	PRPS with $^{99m}\text{Tc}$ -pertechnetate [1]	24 s		42 s

2.	TSPS with $^{99m}\text{Tc}$ -phytate or $^{99m}\text{Tc}$ -pertechnetate [2,3]	5-6 s		-
3.	TSPS with RBC labelled <i>in vitro</i> with $^{99m}\text{Tc}$ [12]	8-12 s		-
4.	Radionuclide angiocardiology with $^{99m}\text{Tc}$ - pertechnetate [4]	-	$9.2 \text{ s} \pm 1.2 \text{ s}$	-
5.	MRI with Gd-BOPTA [13]	3.03 s		-
6.	Contrast-enhanced ultrasound utilizing different echo-enhancers [14,15,16,17]	6.33 s (BR1) 6.45 s (Sonazoid) 15.27 s (Sonovue) 9.597 s (Levovist)		-
7.	LAS with $^{99m}\text{Tc}$ -HDP (present study data)	20-27 s		9.5-13.5 s
8.	LAS with $^{99m}\text{Tc}$ -pertechnetate (present study data)	-		9-13 s
9.	LR-TMDS with $^{99m}\text{Tc}$ -pertechnetate (present study data)	-		12-15 s

The mean LTT of 24 s of colorectal-absorbed  $^{99m}\text{Tc}$ -pertechnetate was approximately four times longer than the LTT of 5–6 s observed at TSPS by Gao L et al. for  $^{99m}\text{Tc}$ -phytate injected into the spleen [2]. Kuba J and Seidlová V provided time-activity histograms for the liver and precordium following splenic injection of  $^{99m}\text{Tc}$ -pertechnetate during TSPS. The LTT for control subjects, as calculated from these histograms, ranged from 5 to 6 s [3]. Syrota et al. conducted TSPS using *in vitro*  $^{99m}\text{Tc}$ -labeled RBC, administered into the spleen, and observed LTT values ranging from 8 to 12 s in patients without a portosystemic shunt [12].

The significantly shorter TTs through the liver of  $^{99m}\text{Tc}$ -pertechnetate, which is not absorbed from the gut, as observed in TSPS [2,3], and through the lungs, noted at LAS and radionuclide angiocardiology [4], show that  $^{99m}\text{Tc}$ -pertechnetate does not directly cause vasoconstriction in these organs, indicating that other substances are the direct triggers in PRPS. This finding suggests that  $^{99m}\text{Tc}$ -pertechnetate binds to specific VAs during absorption through the colorectal wall, forming  $^{99m}\text{Tc}$ -VA soluble complexes that then activate vasoconstriction in the liver and lungs. The

significantly prolonged RHLT determined at PRPS indicates that the vasoactive properties of  $^{99m}\text{Tc}$ -VA complexes remain the same during their passage through the liver.

W. Wayne Lutt stated that resistance to blood flow in the liver primarily occurs in the hepatic venules. Due to the low gradient, of approximately 6-10 mmHg, between the pressure in the portal and hepatic veins, vasoconstriction activated by VAs in the hepatic venules results in a sharp decrease in portal flow [18]. Our study suggests that VAs released from the gut mucosa induce vasoconstriction in the hepatic venules, significantly decreasing the flow velocity through sinusoids and thereby facilitating the elimination of PHCs by Kupffer cells. The arterial inflow is only slightly affected by the increased pressure in post-sinusoidal venules activated during the passage of PHC-VA complexes, due to the high mean pressure in the hepatic artery, which is similar to that in the aorta [19]. Other mechanisms may be activated in the hepatic sinusoids, some of which help reduce portal flow velocity [20,21,22,23,24]. Similarly, the VAs cause vasoconstriction in pulmonary arterioles, significantly decreasing flow through the pulmonary capillaries passed by PHC-VA complexes, thereby improving removal by the lungs' mononuclear phagocyte system [25].

The vasoactive response occurs only in the small vessels of the liver and lungs that are crossed by  $^{99m}\text{Tc}$ -VA complexes. In the liver, vasoconstriction can be triggered in many of the approximately 50,000 post-sinusoidal venules. The liver acts as an essential hemodynamic buffer, and a temporary reduction in blood flow can accompany a significantly decreased velocity of the radiotracer between the portal and hepatic veins. In contrast, the increase in RHLT to 42 s determined in PRPS cannot be attributed to blood flow but solely to  $^{99m}\text{Tc}$ -pertechnetate, as such a sudden and significant decrease in transpulmonary blood flow velocity would cause shock. The  $^{99m}\text{Tc}$ -VA complexes traverse and induce vasoconstriction in only a small percentage of the millions of pulmonary arterioles, leaving the overall blood flow velocity through the lungs unchanged.

$^{99m}\text{Tc}$  and its derivatives are safe radiotracers that are well tolerated after intravenous administration. However,  $^{99m}\text{Tc}$ -pertechnetate, a synthetic compound, is recognized by the body during colorectal absorption as a foreign entity and thus a PHC; consequently, the vasoactive first-pass defense response is triggered against it in the liver and lungs.

An increase in RHLT is not observed in LR-TMDS, where  $^{99m}\text{Tc}$ -pertechnetate is not absorbed through the mucosa. This suggests that the VAs that bind to  $^{99m}\text{Tc}$ -pertechnetate and directly activate hepatic and pulmonary anti-PHC vasoconstriction in PRPS are released from the colorectal mucosa.

*The body should activate this defense response against foreign substances identified as PHCs throughout the digestive tract, where absorption occurs. The uptake of  $^{99m}\text{Tc}$ -pertechnetate in the gastric mucosa interferes with dynamic PRPS-like studies of the stomach; therefore, alternative imaging methods are necessary to detect the presence of the anti-PHC mechanism in both the stomach and small intestine.*

*Various oral medications and food components can activate the anti-PHC mechanism, reducing their bioavailability by increasing elimination. Substances absorbed from the gastrointestinal tract that activate the anti-PHC response temporarily decrease blood flow velocity through the liver and selectively in the lungs. This weakens the shear forces and raises the risk of hepatic and possibly pulmonary metastases in patients with different types of cancer [26], who should avoid foods or oral medications that may contain substances the body could recognize as PHCs.*

PRPS and TSPS conducted with  $^{99m}\text{Tc}$ -pertechnetate in dogs and cats showed a longer LTT in PRPS (average: 12 s in dogs and 14 s in cats) compared to TSPS (average: 7 s in dogs and 8 s in cats) [27,28,29]. This suggests that PHCs absorbed through the colorectal mucosa activate a first-pass vasoactive response in the livers of other mammals, not just in humans.

We note that in our study, we could not assess the intraindividual reproducibility of the data due to strict radiation protection guidelines that prevent repeating nuclear medicine investigations at short intervals without a specific clinical reason. However, the accuracy of data interpretation is supported by the low interindividual variability of TTs. The ranges of LTT and RHLT values in PRPS were three to four times higher than those seen in other imaging studies, with the differences in TTs showing high statistical significance ( $P < 0.0001$ ).

### *1.1. Activation of the Hepatic Vasoactive Response to PHCs Reaching the Gut Mucosa via Arterial Flow Demonstrates its Overall Role in Aiding the Removal of PHCs from the Circulating Blood*

A separate analysis was performed to assess whether the vasoactive response is triggered by PHCs that reach the gut mucosa through arterial flow after intravenous administration. This evaluation was essential to determine if the activation of the anti-PHC mechanism happens during the repeated recirculation of PHCs following their absorption from the gut or if they unintentionally enter the bloodstream.

The LTT values ranged from 22 to 27 s for the radiotracer injected intravenously at LAS, matching the mean value of 24 s observed at PRPS. This supports the idea that the vasoactive response is triggered in the liver by PHCs from the portal flow, which had previously reached the digestive mucosa via arterial blood. Additionally, the similar range of LTT values at PRPS and LAS indicates a comparable strength of the vasoactive responses caused by PHCs absorbed from the gut or delivered to the gut mucosa through arterial blood. This suggests that the vasoactive mechanism we describe acts not only as a first-pass defense against PHCs absorbed from the gut but also as a broader process that helps remove substances recognized as PHCs from circulating blood.

Further research is required to determine whether the body identifies specific imaging agents as PHCs and activates vasoactive defense responses of varying intensities against them. This consideration arises from the significant variations in the mean portal vein to hepatic veins TTs observed in contrast-enhanced ultrasound following the intravenous administration of different echo-enhancers: 6.33 s for BR1 [14], 6.45 s for Sonazoid [15], 15.27 s for Sonovue [16], and 9.597 s for Levovist [17]. The strengths of the vasoactive responses and, consequently, the LTTs probably depend on the chemical properties of the substances identified as PHCs in the intestinal mucosa.

### *1.1. Pathological Activation of the Anti-PHC Mechanism by VAs Released from Primary Tumors and Disseminated Cells Likely Facilitates Early Metastasis of CRC*

During the early development of CRC liver metastases, an increase in the hepatic perfusion index (HPI) measured at LAS, along with a similar Doppler perfusion index (DPI) calculated via ultrasound, is primarily caused by a reduction in portal flow [30,31,32]. This phenomenon is attributed to circulating vasoactive agents [33,34,35,36]. Elevated HPI and DPI have shown high diagnostic value for detecting occult liver metastases in early CRC metastasis [37,38,39,40,41]. The decrease in portal inflow during the initial stages of CRC liver metastasis resembles the increase in LTT and the reduction in portal flow velocity triggered by the anti-PHC mechanism, as noted in PRPS or LAS.

Specific substances released from the colorectal mucosa are crucial for both the anti-PHC vasoactive response highlighted at PRPS and the early metastasis of CRC. More than ninety percent of CRCs originate from the mucosal layer, which our study indicates typically secretes VAs that can enter the portal circulation. The release of VAs from primary CRC tumors into portal tributaries likely relates to the impairment of the gut vascular barrier [42]. VAs trigger the anti-PHC vasoactive response, reducing portal flow velocity, which weakens shear forces [26] and promotes metastasis. Besides vasoconstriction, narrowing of small vessels through other mechanisms may also promote early CRC metastasis by reducing flow velocity in the sinusoids and post-sinusoidal venules [43,44]. No increase in HPI was observed in occult liver metastases from extraintestinal cancers [7]. Our analysis suggests that these cancers do not reduce portal flow during early liver metastasis because they do not produce VAs and, therefore, do not activate the anti-PHC mechanism.

During the establishment of CRC liver metastasis, portal flow is likely reduced by the vasoactive response triggered by VAs, accompanied by a moderate increase in hepatic arterial flow due to the hepatic artery buffer response. During the progression of metastases, which is sustained by neovascularization, portal flow remains reduced as primary tumors continue to release VAs. Hepatic arterial flow gradually increases, becoming the main cause of the abnormal rise in HPI when the diameter of CRC metastases exceeds 2 mm [45]. The increased arterial flow leads to notable enhancements in HPI or DPI for patients with clinically overt liver metastases from either colorectal

or extraintestinal cancers [33,46,47]. CRC metastatic emboli, having detached from the colorectal mucosa and adhered to sinusoids or venules, can release VAs *in situ*, triggering the anti-PHC mechanism. Consequently, even after surgical removal of the primary tumor, HPI and DPI levels remain elevated in patients with occult CRC metastases. [48].

Additional research is required to examine the potential activation of the anti-PHC response during the early metastasis of gastrointestinal tract cancers beyond CRC, considering the initial increase in DPI and HPI observed in gastric and esophageal cancers [37,49,50].

## Limitations

This study has several limitations. Additional research is needed to identify the VAs. Our analysis indicates that VAs can be extracted from portal blood flow after the per-rectal administration of  $^{99m}\text{Tc}$ -pertechnetate. LR-TMDS was conducted with a small patient cohort. We were unable to perform upper rectum transmucosal dynamic scintigraphy using  $^{99m}\text{Tc}$ -pertechnetate or per-rectal portal scintigraphy with radiopharmaceuticals other than  $^{99m}\text{Tc}$ -pertechnetate. Further research is required to determine whether PHCs reaching the gut mucosa through arterial flow can trigger the anti-PHC response in the lungs.

## Conclusions

This study revealed that a first-pass vasoactive response is triggered in the liver and lungs during PRPS to facilitate the removal of  $^{99m}\text{Tc}$ -pertechnetate, an artificial substance that the body recognizes as PHC during colorectal absorption. VAs released from the gut mucosa likely bind to PHCs, forming soluble complexes that directly activate an intense vasoactive response in the liver and lungs, significantly slowing PHC flow. This defense response also activates in the liver against unknown substances that reach the gut mucosa through arterial flow, aiding in the removal of PHCs from circulating blood.

A similar sudden drop in portal flow occurs in the early stages of CRC liver metastasis. CRC cells originating from the mucosa usually produce VAs, which are released into portal tributaries during tumor progression. The VAs cause vasoconstriction, which reduces portal flow velocity and facilitates metastasis. Extraintestinal cancers typically do not produce VAs and, as a result, do not trigger the anti-PHC response.

This study has implications for pharmacokinetics, toxicology, and the food industry, and it may also benefit oncology, especially in the treatment of CRC. Tracking VAs in the bloodstream could aid in the early diagnosis and prompt treatment of CRC with a high metastatic risk. Using specific medications to target VAs or their receptors might inhibit or reduce liver and possibly lung metastasis, potentially extending life expectancy for CRC patients.

**Supplementary Materials:** Supporting information can be provided by the corresponding author upon request.

**Author Contributions:** Dragoteanu M. coordinated the nuclear medicine procedures, conceptualized the study, examined the data collected, reviewed the literature, analyzed the laboratory database, and assessed liver and pulmonary transit times during per-rectal portal scintigraphy, identifying the slowdown in blood flow through the liver and lungs in response to potentially hazardous chemicals passing through the gut mucosa. He examined the role of this mechanism in facilitating early metastasis of colorectal cancer and oversaw the drafting and revision of the manuscript. Tolea S. prepared the manuscript for submission and checked the language as a native speaker. Duca I. compared the data with that from primary liver tumors studied using liver angioscintigraphy and participated in revising the manuscript. Mititelu R. contributed to the synthesis, literature review, and drafting of the manuscript. Kairemo K. supervised the final content and revision. All authors have read and approved the final version of the manuscript.

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## Abbreviations

We used the following abbreviations in the manuscript:

CRC	colorectal cancer
DPI	Doppler perfusion index
HDP	hydroxyethylene-diphosphate
HPI	hepatic perfusion index
LAS	liver angioscintigraphy
LR-TMDS	lower rectum transmucosal dynamic scintigraphy
LTT	liver transit time, from the portal vein to the right atrium
MRI	magnetic resonance imaging
PHC	potentially hazardous chemical
PRPS	per-rectal portal scintigraphy
RHLT	right heart to the liver circulation time
TSPS	trans-splenic portal scintigraphy
TTs	transit times
VAs	vasoactive agents

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