Possible role of the scintigraphic estimation of the relative liver perfusion in the diagnosis and therapy of liver carcinomas

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Background: The aim of the study is evaluation of the possible role of the scintigraphic estimation of the relative liver perfusion in the choice of treatment of liver carcinomas.

Material and methods: Hepatic perfusion index was obtained by dynamic scintigraphy in 126 patients. Results: In the control group values did not differ from the value in the patients with benign tumors (p>0.05). However, in hepatocellular carcinoma and liver metastases of different tumors, HPI values were significantly decreased in comparison to controls and benign tumors (p<0.01), but they didn’t differ between themselves (p>0.05). The values were especially low in the patients with malignant diseases in the liver associated with vascular disturbances in the portal system. Conclusion: HRA could be easily done during the different conventional nuclear medicine methods. It can be an useful method for the assessment of different degrees of hemodynamic alterations in portal system, for differential diagnosis of benign and malignant liver tumors, as well as for assessment of the liver tissue and tumor perfusion, which might be helpful in the decision making for the undertaking of intraarterial (radionuclide, chemotherapy etc.) therapy.

Key words: hepatic radionuclide angiography, liver tumors, perfusion

INTRODUCTION

Under physiological condition, liver is supplied with approximately 30% of the arterial and 70% of the venous blood. Considering the fact that the change of the relative arterial and venous component contribution is caused by different pathological changes (portal hypertension, malignant tumors, vascular disturbances) it is very important to chose appropriate method for the estimation. Studies of the liver blood flow play an important role in the evaluation of hemodynamic disorders encountered in various hepatic diseases.

In the preevaluation and diagnosis of the patients with liver tumors, after ultrasonography and Doppler-US significant nuclear medicine methods are used: radiocolloid, blood pool, hepatobiliary scintigraphy, angioscintigraphy with radiolabeled microspheres as well as “first pass” radionuclide angiography. These methods precede selective angiography and other invasive methods. CT and nuclear magnetic resonance, although used mainly for the morphological examination of the liver can be also performed in hepatic blood flow studies. Recently, positron emission tomography is also included, in the combination with other imaging modalities.

Nuclear medicine methods are basically founded on the analysis of hepatic radionuclide angiogram (HRA), obtained after the "first pass" of the radioactive bolus and registered activity over liver and other abdominal organs after intravenous injection of 99mTc. Besides the methods based on the assessment on the total liver blood flow and assessment of shunts, the technique of radionuclide angiography and determination of the hepatic perfusion index (HPI) proposed by Sarper is noninvasive method supplying well reproducible information on portal blood flow.

The aim of the study is evaluation of the possible role of the scintigraphic estimation of the relative liver perfusion in the choice of treatment of liver carcinomas.

PATIENTS AND METHODS

The study was performed in 126 patients: 24 controls (C), 45 with benign liver tumors (BT) (30 hemangiomas, 7 adenomas and 8 focal nodular hyperplasias), 15 with hepatocellular carcinomas (HCC) and 57 with metastases of different carcinomas in the liver (MLC) (29 colorectal carcinomas, 7 lung carcinomas, 3 bronchial carcinomas, 5 breast carcinomas, 8 lymphomas and 5 melanomas). In the HCC group, there were 4 patients and in MLC group 22 patients without vascular disturbances in the portal system. However, in the HCC group, 3 patients had cavern-
ous portal vein developed after tumor thrombosis, 3 had complete thrombosis and 5 had incomplete thrombosis (2 with thrombosis of the either of the portal venous branches and 3 with thrombosis of the main lumen of the portal vein. In the MLC group, 5 patients had cavernous portal vein developed after tumor thrombosis, 9 had complete portal venous occlusion and 11 incomplete thrombosis (thrombosis of the either of branches).

HRA was performed with bolus injection of 740 MBq $^{99m}$Tc-pertechnetate, (1 min, 1f/s), using ROTA scintillation camera. From the ROI over liver parenchyma, TA arterial and portal-venous phase of the HRA, were separated at the moment when maximal activity over the left kidney ROI was registered.

Arterial (Ba) and portal (Bp) slopes were determined and hepatic perfusion index (HPI) calculated according to Sarper’s method (HPI=Bp/(Ba+Bp), (10). Thus, hepatic perfusion index reflects the value of the relative portal contribution to the liver blood flow. The final diagnoses were based according to the clinical findings, results of the functional and laboratory analysis, ultrasound and Doppler ultrasound, angiography, biopsy with histopathology and other clinical examinations. Consent was obtained from each patient, and the study protocol conforms to the established ethical guidelines.

RESULTS

In C, HPI was $0.68\pm0.06$ which did not differ from the value in BT ($0.64\pm0.08$) ($p>0.05$) (Figure 1). However, in HCC ($X=0.26\pm0.20$) without vascular disturbances in the portal system, and MLC without vascular disturbances in the portal system, ($X=0.40\pm0.28$), HPI values were significantly decreased in comparison to C and BT ($p<0.01$), but they didn’t differ between themselves (HCC-MLC, $p>0.05$).

In 3/15 HCC with cavernous portal vein developed after tumor thrombosis values were nonsignificantly lower ($X=0.20\pm0.12$, $p<0.05$) than in HCC without vascular disturbances in the portal system. However, in comparison to HCC without vascular disturbances in the portal system, in 3 HCC patients with complete thrombosis (HPI=0, $p<0.01$) and in 5 HCC with thrombosis of the either of portal venous branches and/or incomplete portal venous thrombosis (HPI=$0.17\pm0.09$, $p<0.05$) values were significantly lower (Figure 2).

In 5/57 patients with MLC and cavernous portal vein developed after tumor thrombosis, HPI was nonsignificantly lower than in MLC ($X=0.32\pm0.17$, $p>0.05$) without vascular disturbances in the portal system. However, in comparison to MLC without vascular disturbances, in 9 MLC patients with complete portal venous occlusion (HPI=0, $p>0.01$) and in 11 MLC with thrombosis of the either of branches, values were significantly lower (HPI=$0.25\pm0.03$, $p<0.05$) (Figure 3).

DISCUSSION

In C, HPI values did not differ from the value in BT ($p>0.05$). However, in HCC without vascular disturbances in the portal system, and MLC without vascular distur-

![FIGURE 1. PATIENT WITH HEMANGIOMA.](image)

A) HEPATIC RADIONUCLIDE ANGIOGRAPHY ($^{99m}$Tc-PERTEHNETATE): LIVER CURVE, AFTER "FIRST PASS" OF RADIOPHARMACEUTICAL, HAS THE PHYSIOLOGICAL SHAPE AND IT IS POSSIBLE TO DIFFERENTIATE TWO PHASES WITH PHYSIOLOGICAL VALUE OF THE RELATIVE LIVER PERFUSION (HPI=0.71).

B) PLANAR LIVER SCINTIGRAPHY ($^{99m}$Tc-SN-COL-LOID), POSTERIOR VIEW (LEFT) SHOWS "COLD" LESION IN THE POSTERIOR PART OF THE RIGHT LIVER LOBE, WHILE DELAYED BLOOD POOL SCINTIGRAPHY ($^{99m}$Tc-RED BLOOD CELLS) SHOWS THE "HOT SPOT" IN THE SAME PLACE.
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FIGURE 2. PATIENT WITH HEPATOCELLULAR CARCINOMA.
A) HEPATIC RADIONUCLEIDE ANGIOGRAPHY (99MTC-PERTHNETATE): LIVER CURVE, AFTER "FIRST PASS" OF RADIOPHARMACEUTICAL, SHOWS INCREASED ARTERIAL PARTICIPATION IN THE BLOOD FLOW (VERY STEEP AND PROLONGED ARTERIAL PHASE), AND CONSECUTIVELY DIMINISHED PORTAL PERFUSION (HPI=0.35).
B) PLANAR LIVER SCINTIGRAPHY (99MTC-SN-COLLOID), RIGHT LATERAL VIEW (LEFT) SHOWS "COLD" LESION IN THE UPPER LATERAL PART OF THE RIGHT LIVER LOBE, WHILE DELAYED BLOOD POOL SCINTIGRAPHY (99MTC-RED BLOOD CELLS) SHOWS ALMOST ISOVASCULARISED TISSUE WITH THE LIVER PARENCHYMA IN THE SAME REGION.

(30% towards 70%) and that radionuclide angiography can be performed in the estimation of the liver perfusion. In benign tumors of the liver, this relationship remains unchanged. On the contrary, in malignant tumors, primary or metastatic liver tumors, occurs the significant increase of the arterial component of the liver vascularityization. An additional reduction of the portal flow occurs in the presence of portal thrombosis in the proportion to the degree of occlusion. Thus, in the complete portal venous thrombosis, venous blood flow through the liver is not registered at all (HPI=0). In the patients with cavernous transformation of the portal vein, where the place of the thrombosis is bypassed and portal inflow reestablished, HPI values are not different from the values in the patients with malignant tumors, primary and metastatic, without vascular disturbances in the portal system.

The results of other authors are in accordance with our findings. Thus, according to Petroviæ et al. 14, determined in total liver parenchyma, HPI is a sensitive indicator of the presence of malignant liver tumors, but is within normal range in patients with hepatic hemangioma. According to him, portal venous inflow of some angiomatos liver lesions in infants and children, and arterio-portal shunting in hemangiomas are rare. Results of his study indicate that regional determination of hepatic perfusion index and other HRA parameters in patients with focal liver lesion enables differentiation between tissues with different intensity and pattern of blood flow. The method could be used in examination of vascularisation pattern of other focal liver lesions. The results of Dragoteanu et al. 15 showed that malignant tumors (primary or metastases) increase the arterial supply of the liver and decrease the portal flow. On the contrary, benign tumors do not change portal/arterial liver blood flow ratio. However, liver cancer occurring on cirrhosis which also causes vascular disturbances in the liver parenchyma is a limiting factor for liver angiocintigraphy. Hepatic metastases increase the arterial perfusion before their size allows morphologic imaging diagnosis, and liver angiocintigraphy is therefore an early method to diagnose liver metastases especially in colorectal cancer. According to Muroff et al. 16 radionuclide angiography is an established, widely used diagnostic tool, because it is safe, easy to perform, and the low patient radiation dose makes frequent follow-up studies feasible. According to this author, hepatic tumors can be differentiated from cysts with radionuclide angiography. Similarly, the prevalence of the arterial component of the blood supply and the lessening of the blood supply value by 40-50% in loci of the lowered accumulation of a colloidal radiopharmaceutical only with the preserved blood flow in the adjacent tissues are characteristic of primary tumor or metastatic involvement of the liver 17. Rudberg et al. 18 using radionuclide angiography, found a generalized increase of arterial blood flow to the liver in alcoholic liver disease and metastatic liver disease. He concluded that generalized increase of arterial blood flow to the liver is a clinically important finding that could escape detection if radionuclide angiography is not included in the RIS scintigraphy. Shiomi et al. 19 examined the usefulness of factor analysis for the diagnosis of hepatocellular carcinoma by analysis of the data obtained by radionuclide angiography. In patients with hepatocellular carcinoma, the factor of the tumor is included in the arterial phase, so that the cancerous region could be differentiated from the noncancerous region. The ratio of the radioactivity of the cancerous region to the noncancerous region was used to estimate the blood flow of the tumor region. Belfer et al. 20 presented a case of a benign hepatic-cell adenoma studies with dynamic radionuclide angiography and static imaging with different tracers. Rarely, angiocintigraphic findings can be false positive. Thus, two cases of actinomycosis, in which hypervascular hepatic masses were observed in the arterial phase of radionuclide angiography are reported14.

Some recent papers employ positron emission tomography for the assessment of the liver tumor perfusion using inhaled C15O2. Dynamic PET measurements of regional flow are reproducible in patients with predominantly intra-abdominal malignancies and may be useful for the pharmacodynamic evaluation of novel antivascular and antiangiogenic cancer therapeutic agents22. Also, consid-
ering that growth of malignant tumors is dependent on sufficient blood supply, an enhanced microvessel density is seen as part of these reactions and is associated with increased perfusion as measured by PET. Blood flow in metastatic colorectal carcinoma calculated quantitatively by PET scanning using the $^{15}\text{CO}_2$ steady-state method and the $\text{H}_2^{15}\text{O}$ dynamic method, showed results almost parallel with the angiographic ones. These findings suggest that blood flow in hepatic metastases from colorectal carcinoma is greater than generally is believed.

Some authors used PET and CT in the investigation of liver tumor blood flow and metabolism. Thus, total hepatic blood flow estimated by CT and glucose metabolism estimated by PET are two distinct but related biologic correlates for liver texture on portal phase CT, which can be used as an indicator for patients with colorectal cancer. Also, Wang et al. suggests significant mean reduction of hepatic metastatic tumor load (metabolism), as evaluated objectively by PET after $^{90}\text{Y}$-microspheres treatment of unresectable liver metastatic disease. Some authors employ CT angiography to delineate the blood supply and volume to a targeted hepatic segment, allowing superslective $^{90}\text{Y}$ radioembolization. In addition, Sato et al. used $^{90}\text{Y}$-microspheres as a primary treatment option for primary and secondary hepatic malignancies (hepatocellular carcinoma and metastatic liver disease) and followed the results by angiography.

Radionuclide angiography may be helpful to evaluate the therapeutic effect of hepatic arterial embolization. Radionuclide $^{99m}\text{Tc}$-MAA (macroaggregates of albumin) angiography appears to be an accurate method for demonstrating successful embolization of the vascular supply in hepatocellular carcinoma. Also, percutaneous arterial embolization of a vessel to correct liver misperfusion shown by nuclear scintigraphy is safe and effective and may be used for treating primary and metastatic carcinoma of the liver. In addition, fusion imaging using the combined SPECT/CT system reflects the actual distribution of the infused anticanancer agent. This information is valuable also for avoiding potential extrahepatic complications.

RI-angiography with $^{99m}\text{Tc}$-MAA plus degradable starch microspheres (DSM) revealed the increased accumulation in the tumor, compared to $^{99m}\text{Tc}$-MAA only, which indicates that intra-arterial chemotherapy combined with mitomycin C and DSM achieve higher regional selectivity. Kaplan et al. concluded that radiotracers introduced at flow rates approximating those attained with infusion pumps will offer the best estimates of both initial catheter placement and subsequent patterns of hepatic distribution of chemotherapeutic agents. However, although hepatic artery perfusion scintigraphy is the primary tool for evaluation of hepatic perfusion after catheter placement, angiography plays an important role in treating the subset of patients with unsatisfactory hepatic perfusion. Also, perfusion of extrahepatic organs or asymmetric liver perfusion (i.e., "misperfusion") can be diagnosed by nuclear scintigraphy and precludes the use of hepatic arterial infusion pump for the infusion of chemotherapy agent. In addition, angioscintigraphy evaluation of the liver perfusion with three radioactive compounds: standard

**CONCLUSION**

HRA could be easily done during the different conventional nuclear medicine methods used in diagnostic process and in the pre-treatment or post-treatment evaluation. In addition, it can be an useful method for the assessment of different degrees of hemodynamic alterations in portal system, for differential diagnosis of benign and malignant liver tumors, as well as for assessment of the liver tissue and tumor perfusion, which might be helpful in the deci-
on making for the undertaking and monitoring the effect of intraarterial (chemotherapy, embolization, as well as radionuclide) therapy.

It is particularly suggestible because of the fact that this therapy is mainly recommended in the unselected and untransplantable patients with portal venous occlusion and mainly arterial vascular supply. Thus, by this non-invasive method, it could be able to avoid invasive and complicated (especially in the patients with impaired coagulation factors) recommended study of portal backflow by injection of an iodinated hydroxosoluble radiological contrast agent into the splenic or superior mesenteric artery, which is a preliminary study for the selection of the patients for radionuclide intraarterial therapy. It could also be used for evaluation of the efficacy and safety of hepatic intraarterial radionuclide therapy in the treatment of liver carcinomas in patients with impaired portal venous flow, for the evaluation of its effect on the tumor itself, as well as its effect on the tumor thrombi in the portal vein which are also arterially vascularized.

This method will also allow the selection of the patients on the basis of tumor vascularisation, and reject from the procedure those (minority) with predominantly portal vascularisation, or mainly arterial but with insufficient supply. Also, this procedure will allow the exact estimation of the portal venous occlusion, suggestible for the procedure.

SUMMARY

**POTenCIJALNA ULOGA SCINTIGRAFSKE PROCENE RELATIVNE PERFUZIJE JETRE U DJAGNOSTICI I TERAPIJI KARCINOMA JETRE**

Cilj: Cilj rada je procena potencijalne uloge scintigrafske procene perfuzije jetre u dijagnozi i izboru lečenja carcinoma jetre.

Bolesnici i metode: Hepatički perfuzioni indeks je određen posle dinamske scintigrafije u 126 pacijenata.

Rezultati: U kontrolnoj grupi vrednosti se ne razlikuju od onih u pacijenata sa benignim tumorima (p<0.05). Ipak, u hepatocelularnom karcinomu i metastazama različitih tumora u jetri, HPI vrednosti su značajno snažene u poređenju sa kontrolnom grupom i bolesnicima sa benignim tumorima (p<0.01), ali se ne razlikuju medusobno (p>0.05). Vrednosti su posebno niske u bolesnika sa malignim bolestima jetre udruženim sa vaskularnim poremećajima u portnom sistemu.

Zaključak: HRA se može jednostavno uraditi u toku različitih metoda nuklearne medicine. Dodatno, može biti korisna metoda za procenu hemodinamskih poremećaja u portnom sistemu različitog stepena, za diferencijalnu dijagnostu benignih od malignih tumorama, kao i za procenu perfuzije tkiva jetre i tumora, što može biti korisno u donošenju odluke za preduzimanje intrarterijske (radionuklidne ili hemo) terapije.

Ključne reči: hepatich bra radionukleidna angiografija, tumor jetre, perfuzija

REFERENCES


NAPOMENA
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