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Original Article

Dynamic PET with ^{18}F-Deoxyglucose (FDG) and quantitative assessment with a two-tissue compartment model reflect the activity of glucose transporters and hexokinases in patients with colorectal tumors

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Abstract: Dynamic PET (dPET) with ^{18}F-Deoxyglucose (FDG) provides quantitative information about distribution of the tracer in a predefined volume over time. A two-tissue compartment model can be used to obtain quantitative data regarding transport of FDG into and out of the cells, phosphorylation and dephosphorylation rate of intracellular FDG, and fractional blood volume in the target volume, also named vessel density. Aim of the study was the correlation of glucose transporters expression and hexokinases with the corresponding compartment parameters. Patients with colorectal tumors were examined with dynamic PET prior to surgery. Afterwards, tumor samples were obtained during surgery and gene expression was assessed using gene arrays. The dynamic PET data were evaluated to quantify the parameters of a two tissue compartment model for colorectal tumors using a Volume-of-Interest (VOI) technique. A multiple correlation/regression analysis was performed using glucose transporters as independent variables and k_1 as the dependent variable. A correlation of r=0.7503 (p=0.03) was obtained for the transporters SLC2A1, SLC2A2, SLC2A4, SLC2A8, SLC2A9, SLC2A10 and k_1. The correlation of r=0.7503 refers to an explained variance of data of 56.30 %, therefore more than 50 % of data changes are associated with the gene expression. An analysis of the hexokinases HK1-HK3 and k_3 revealed a correlation coefficient of r=0.6093 (p=0.04), which is associated with an explained variance of 37.12 %. Therefore, parameters k_1 and k_3 reflect gene activity. The results demonstrate that k_1 and k_3 of the two-tissue compartment model are correlated with glucose transporters and hexokinases.

Keywords: Dynamic PET, compartment model, glucose transporter, hexokinase

Introduction

The standard radiopharmaceutical for PET examinations of oncological patients is ^{18}F-Deoxyglucose (FDG), especially in patients with colorectal tumors (CRC). It is generally assumed, that FDG is transported into tumor cells via the glucose transporters and phosphorylated by the hexokinases. A two-tissue compartment model can be used e.g. to obtain quantitative data about the transport and phosphorylation of FDG, provided that dynamic PET data were acquired, usually for a time interval of 60 minutes following tracer application. Moreover, a quantitative Volume-of-Interest (VOI) based analysis parametric imaging can be performed with these dynamic data [1]. We refer to this technique as dynamic PET (dPET) or dynamic PET-CT (dPET-CT). Shortened acquisition protocols may also be applied to the data [2].

Several experimental and patient studies were performed in order to correlate glucose transporter expression and the FDG uptake. Most of these published data are focused on the GLUT-

1 expression exclusively. Tian et al. compared the GLUT-1 expression and maximum SUV in 33 patients with colorectal tumors and noted a low but significant correlation of r=0.428 [3]. However, Hong et al. assessed GLUT-1 expression with maximum SUV in 44 patients with colorectal tumors and noted no significant correlation [4]. Park et al. evaluated 19 patients with malignant melanomas and compared maximum SUV with GLUT-1, GLUT-3, as well as HK-2 and Ki-67 expression in tumor samples using immunochemistry [5]. The authors noted a significant correlation for GLUT-1 and GLUT-3 with maximum SUV. In contrast, Moon et al. compared GLUT-1 expression with the FDG uptake in untreated papillary thyroid carcinoma and found no association for GLUT-1 expression and tracer uptake [6]. These results suggest that the overall tracer uptake, as measured by the average or maximum SUV, may not be necessarily dependent on the expression of GLUT-1.

The intracellular FDG transport can be quantified, if a dynamic PET acquisition is performed and a two-tissue compartment model is applied to the dynamic data. Thus detailed quantitative information is obtained about FDG metabolism. Usually, five parameters are obtained: vb, the fractional blood volume or vessel density, k_1 and k_2, the transport parameters (influx and efflux), and k_3 and k_4, the parameters reflecting phosphorylation and dephosphorylation. A simplification of the model consists of the summary of interstitial and cellular space. Furthermore, an input function is required. Little is known about the correlation of k_1 with genes associated with glucose transport as well as k_3 and genes linked to the phosphorylation of intracellular glucose.

Only a limited number of studies have been performed in oncological patients using a dynamic data acquisition and only a few studies applied a two-tissue compartment model to FDG kinetics. Therefore, the correlation of glucose transporters and k_1 in patients remains not clear. Besides FDG transport into the cells, intracellular phosphorylation via the hexokinases is important for the tracer uptake and accumulation. Park et al. evaluated also HK-2 in melanoma patients, but found no correlation with the uptake [5]. The authors note, that HK-2 does not play a role for the global FDG uptake. However, no comparison was made to k_3. In contrast, Kaira et al. evaluated GLUT-1, HK-1, HIF-1a, VEGF, and CD34 in patients with metastatic pulmonary tumors and found a dependency of the FDG uptake on HK-1 [7]. There is also a patient study from Okazumi et al., who correlated k3 with the hexokinase activity [8]. Haberkorn et al. evaluated the correlation of the FDG uptake with GLUT-1 and hexokinase expression in several animal tumors [9]. In contrast to other studies, he found a correlation of r=0.83 for GLUT-1 and FDG uptake and r=0.87 for the hexokinase and the uptake values. No model was applied to the data. Overall, little is known about the expression of hexokinases and k_3 of the 2-tissue compartment model in patients.

The published results suggest, that GLUT-1 may not be the only gene, which is associated with FDG uptake, but other genes may play even also a role. Therefore, the correlation of multiple glucose transporters and k_1 of the 2-tissue compartment model was evaluated in this study. Furthermore, we correlated k_3 with the expression of several hexokinases.

Materials and methods

Patient data and PET acquisition

The study comprises 25 patients with colorectal tumors, scheduled for surgery. The gene array data set had been previously analyzed to assess the association of tracer kinetics and angiogenesis related genes as well as genes correlated with proliferative activity [10, 11]. PET studies were performed within two days prior to surgery. The PET system (ECAT EXACT HR+; Siemens) provided an axial field of view of 15.3 cm and was operated in 2-dimensional mode. The maximum number of slices was 63, with a theoretic slice thickness of 2.425 mm. A 10-min transmission scan preceded the dynamic series and was used for the correction of the dynamic emission data. Generally, a dynamic data acquisition is performed at our center for all PET examinations with FDG. The patient is positioned to acquire data from the region of the primary tumor, which is already known and histologically verified prior to PET. Following the injection of 250-370 MBq FDG, data are acquired for one hour. The iterative reconstruction comprises 28 frames with increasing times per frame. The quantitative evaluation is performed with a dedicated soft-

Table 1. Quantitative data obtained from the gene arrays for the glucose transporters (values expressed in REV)

parameter	SLC2A1	SLC2A2	SLC2A3	SLC2A4	SLC2A5	SLC2A6	SLC2A8	SLC2A9	SLC2A10
mean	115.03	0.32	14.72	3.13	15.06	4.16	18.24	23.09	29.32
sd	41.44	0.15	19.74	1.75	6.64	3.77	9.85	8.01	17.70
median	111.29	0.28	5.07	2.77	13.43	2.42	14.94	22.90	24.67
no.	24	24	24	24	24	24	24	24	24

Table 2. Quantitative data obtained from the gene arrays for the hexokinases (values expressed in REV)

parameter	HK1	HK2	HK3	HK4
mean	96.29	85.65	1.58	5.60
sd	30.57	29.91	0.87	2.93
median	89.81	75.48	1.39	5.04
no.	24	24	24	24

ware developed from our project group. VOIs are placed over the tumor, a reference area (normal colon), and a large vessel, usually the descending aorta. The VOI´s of the aorta were used for the calculation of the input function. A 2-tissue compartment model is fitted to the data obtained by the time activity curves of the VOIs using a software, which is based on a modified machine-learning algorithm (SVM) [12]. Details of the PET data acquisition and evaluation are already described [10].

Tissue specimen and gene arrays

Tissue specimens of the tumor were obtained in 24 patients during surgery. Surgeons already had the information where PET data evaluation was performed and tried to obtain a tissue specimen as close as possible to this anatomic tumor area.

All tissue specimens were processed and a gene array (U133A, Affymetrix Inc.) was used for further evaluation of the gene expression. Overall, this gene array provides quantitative data about 22283 gene probes. The processing of the extracted RNA and the gene arrays was done according to the manufacturer's guidelines and details of the processing of the specimens are already described [13]. Finally, the gene expression data were converted to relative expression values (REV) using the formula REV = 1000 * gene expression value / expression value of $ß_2$-microglobulin [13].

Statistical data evaluation

The evaluation of the gene array and PET data was performed with a dedicated software (GenePET) developed by our group [14]. Generally, the major advantage of our software is the interactive and correlative evaluation of large data matrices. Enhanced expressed genes are easily identified due to the two dimensional color coded display of all gene expression data. Statistical evaluation of all results was performed with the multiprocessor version of STATA/MP 12.1 (Stata Corp.) on a Mac Pro (12-core system, 24 GB RAM) (Apple Inc.).

The study was approved by the Ethical Committee of the University of Heidelberg and the Bundesamt für Strahlenshutz according to the german regulations.

Results

The evaluation included gene array data in 24/25 patients. In one patient the tumor specimen could not be used for gene array analysis. The data acquired from dPET could be evaluated by the 2-tissue compartment model in 23/25 patients. In two patients, the region of the surgically obtained tissue specimen was not within the field of view of the dynamic data acquisition on PET and as a result, VOI based analysis was not possible. Therefore, we were able to compare the glucose transporters expression data as well as hexokinases expression data, as derived from dPET studies in 22 patients.

Descriptive statistics

Besides numerous other genes (overall 22283 gene probes per array), gene array data provide information about the facilitated glucose transporter genes. Quantitative data about the following transporters were available for further analysis: GLUT-1 (SLC2A1), GLUT-2 (SLC2A2),

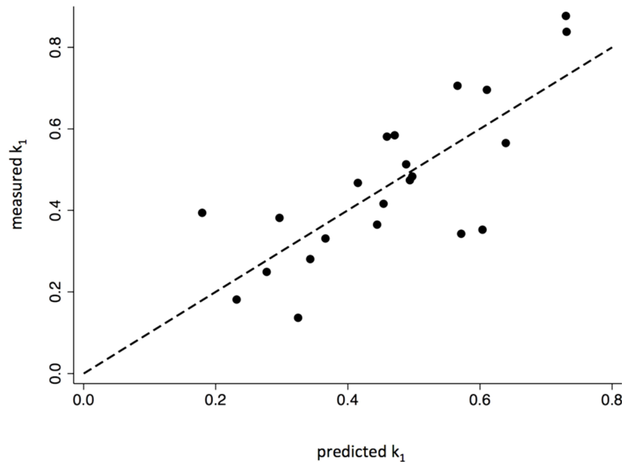

Figure 1. Correlation between the k_1 as measured by FDG dPET and the predicted k_1 as calculated by a multivariate regression analysis based on the combination of the glucose transporters SLC2A1, SLC2A2, SLC2A4, SLC2A8, SLC2A9, and SLC2A10. The correlation coefficient is r=0.7503 (p=0.03). This refers to an explained variance of 56 % of the FDG tracer kinetic curve. Therefore, about 56 % of the FDG tracer curve is dependent on the facilitated glucose gene expression.

GLUT-3 (SLC2A3), GLUT-4 (SLC2A4), GLUT-5 (SLC2A5), GLUT-6 (SLC2A6), GLUT-8 (SLC2A8), GLUT-9 (SLC2A9), GLUT-10 (SLC2A10). The hexokinases (HK) 1-4 were also quantitatively available from the gene array data. The data regarding facilitated glucose transporters are shown in **Table 1**, and those regarding for HK1-4 are demonstrated in **Table 2**. The dPET parameters in the 22 patients, where gene array data as well as PET data were available, revealed a mean k_1 of 0.46 (median: 0.44) and a mean k_3 of 0.11 (median: 0.10).

Correlation analysis

The single parameter linear correlation analysis of the facilitated glucose transporter family 2 member 1 (GLUT-1) (independent variables) and k_1 as the dependent variable did not achieve statistical significance on the p=0.05 level. This was not a surprising result, because of the availability of multiple facilitated glucose transporters in the cells. Therefore, it cannot be expected that just a single transporter alone has an impact on k_1. However, the combination of glucose transporters is likely to have an impact on the compartment parameter. We assume, that the facilitated glucose transporters are generally not really independent variables but dependent on each other on a certain level.

Therefore, a multivariate regression analysis was applied to the data to identify those facilitated glucose transporters, which are primarily associated with k_1. We used the t-values of the parameter estimates for the selection of the most important genes applying a lower limit of t>1.50. A correlation of r=0.7503 (p=0.03) was found for k_1 and the combination of the following facilitated glucose transporters: SLC2A1, SLC2A2, SLC2A4, SLC2A8, SLC2A9, and SLC2A10. The predicted k_1, based on the listed glucose transporters expression, and the measured k_1 are shown in **Figure 1**. The correlation coefficient of r=0.7503 refers to an explained variance of 56 % of the FDG tracer kinetic curve. Therefore, about 56 % of the FDG tracer curve is dependent on the facilitated glucose gene expression.

The single correlation analysis of HK1-4 and k_3 revealed a significant linear correlation for HK1 and k_3 with r=0.4283 (p=0.047). A scatterplot of the data revealed a nonlinear dependency of k_3 on HK1. Therefore, nonlinear functions were fitted to the data. The nonlinear fit with a Gompertzian function revealed a correlation of 0.4999 (**Figure 2**). Again, we can assume that single parameter analysis did not reveal the best correlation/regression results, probably due to the possible dependency on other HKs. Again, we used a multiple correlation analysis and the assessment via the t-values for the individual parameters of the function to identify those HKs, which contribute best to the correlation. The highest multiple correlation was found for k_3 and HK1, HK2, and HK3 with r=0.6093 and p=0.04 (**Figure 3**). While about 56 % of the changes in tracer time-concentration values are dependent on the FDG glucose transporters expression, about 37 % are dependent on the phosphorylation of the intracellular FDG by the hexokinases.

Overall, we were able to demonstrate by the multiple regression analysis, that FDG tracer activity over time, as measured by k_1 and k_3, is dependent on both the facilitated glucose transporter activities and the activities of the hexokinases. These results demonstrate, that k_1 and k_3 of the applied 2-tissue-compartment model are in compliance with the gene expression data. The 2-tissue compartment model is

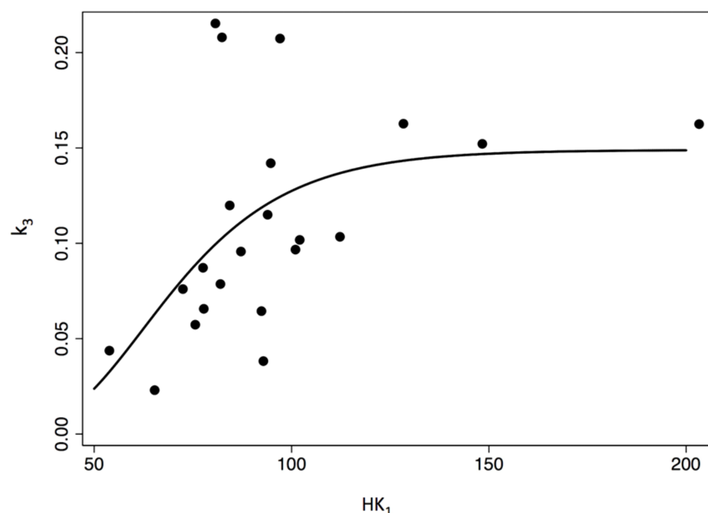

Figure 2. Nonlinear correlation based on a Gompertzian function between the HK1 and k_3. The correlation coefficient is r=0.4999.

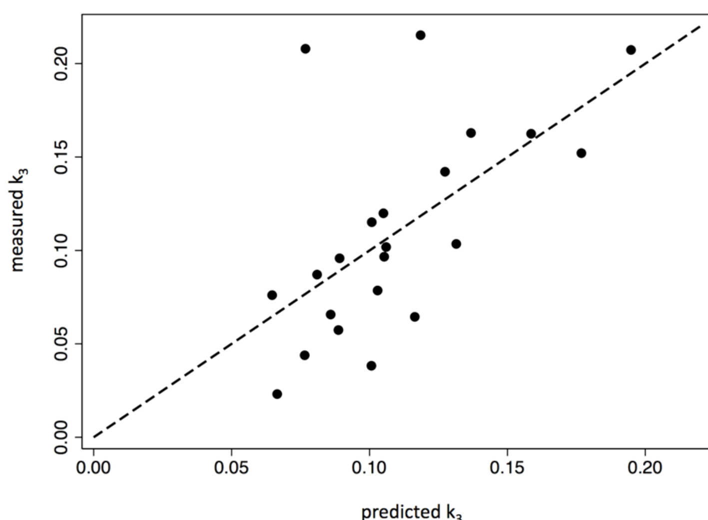

Figure 3. Correlation between k_3 as measured by FDG PET and the predicted k_3 as calculated by a multivariate regression analysis based on the combination HK1, HK2, and HK3 with r=0.6093 (p=0.04). This refers to an explained variance of 37 % of the FDG tracer kinetic curve. Therefore, about 37 % are dependent on the phosphorylation of the intracellular FDG by the hexokinases.

an accurate approach to assess dynamic FDG data and to obtain indirect information about the expression of glucose transporters and hexokinases.

Discussion

The standard approach for quantitative assessment of dPET FDG studies is usually performed by applying a 2-tissue compartment model to the acquired data. One of the first scientists who applied a compartment model to dynamic PET data was Phelps et al. [15]. For years the model had found use primarily for FDG brain examinations including brain tumors and heart studies. Shioya et al. used the compartment modeling to assess FDG metabolism in recurrent meningioma [16].

For global uptake measurements we introduced the term "standardized uptake value (SUV)" in 1991 [17]. The SUV is a parameter for the relative distribution of a tracer, considering the mean tracer distribution in relation to a local measurement: SUV = tissue concentration [Bq/g] / (injected dose [Bq] / body weight [g]). While uptake measurements like the average SUV or maximum SUV provide general information about the local tracer uptake, model based analysis provides much more detailed information regarding FDG kinetics. This can be helpful e.g. for differential diagnostics or follow up examinations, in order to assess the effect of treatment. Dimitrakopoulou-Strauss et al. evaluated the FDG kinetics in 83 patients with bone lesions [18]. Overall, 46 lesions were benign and 37 were malignant tumors. While single parameter analysis with SUV revealed a sensitivity of only 54 % and a specificity of 91 %, the additional use of the full kinetic analysis data enhanced the sensitivity to 76 % and the specificity to 97 %. These data show, that it is generally favorable to use additionally kinetic data for the assessment of PET examinations.

The basic assumption is, that a 2-tissue compartment model reflects the activities of the glucose transporters and hexokinases. Thus the model mirrors genetic activities of these genes. Therefore, it is important to evaluate, if the compartment parameters k_1 and k_3 really reflect the activities of the glucose transporters

and hexokinases. The correlation analysis revealed no significant correlation for the expression of the glucose transporters and k_1, when a single variable analysis was performed. However, due to the availability of multiple glucose transporters it can be assumed, that not just one, but several transporters are important to transfer FDG into the cells. As a consequence, a significant correlation was noted for k_1 and six of the glucose transporters (SLC2A1, SLC2A2, SLC2A4, SLC2A8, SLC2A9, and SLC2A10). We assume that the pattern of glucose transporters correlating with k_1 is dependent on tumor histology. Therefore, these results are valid for colorectal tumors, but not necessarily for tumors with a different histology.

Besides the correlation of k_1 with the glucose transporters a correlation was also found for HK1 and k_3 in the colorectal tumors. Statistical analysis revealed HK1, HK2, and HK3 as primarily significant variables for k_3. The results demonstrate, that k_3 reflects hexokinases activities. Okazumi et al. evaluated FDG kinetics in primary liver tumors and used k_3 and k_4 for the differentiation of hepatocellular carcinoma [8]. The authors determined the hexokinase quantitatively in ten tumors and noted a correlation coefficient of r=0.658 for the hexokinase activity in tumors and k_3. The results are comparable to the correlation of r=0.6093 we found for HK1-3 and k_3.

The fitting of a 2-tissue compartment model is dependent on the input and target data, as well as the algorithm used for fitting. We use for the input a VOI of a large vessel, comprising at least seven contiguous slices. The target volume is evaluated also with a VOI and the size is dependent on the size of the tumor. Usually, the Levenberg-Marquardt or Powell algorithm is used for iterative compartment fitting in most of the programs. One limitation of this algorithm is the sensitivity to noisy data. Other problems are e.g. overfitting resulting in k_x-parameters greater than one, which does not make any sense in biological terms. Frequently, also vb-values nearby zero may be obtained. The iterative fitting demands experienced scientists to perform sequentially fitting of the five compartment parameters.

The SVM algorithm implemented in our software is a predictive approach, based on a database of input and target data as well as the valid corresponding 2-tissue compartment results. Firstly, the actually measured input and target curves are compared to the data in the database, and a nonlinear regression is performed via the SVM algorithm to predict the 2-tissue compartment parameters. Therefore, the results obtained by the SVM algorithm are independent from the person performing the data evaluation. If needed, the results can also be used as an estimate for an iterative compartment fitting, providing more stable results due to the selection of appropriate starting values.

The correlation coefficient of r=0.7503 for k_1 and the glucose transporters refers to an explained variance of the k_1 data of 56.3 %, while for k_3 about 37.1 % of the variance is explained by an existing correlation of k_3 and the hexokinases. These data direct to a generally higher noise level of k_3 as for k_1. However, also the gene array data contain noise. Overall, noise in both, the PET and gene array data, limit the correlation analysis. However, we can conclude, that the 2-tissue compartment model, as applied in this study, is an excellent tool to assess the activities of the facilitated glucose transporters and hexokinases.

New treatment protocols are in use for therapy of colorectal cancer, like antiangiogenic (bevacizumab, aflibercept, regorafenib) or antiproliferative agents (oxaliplatin, irinotecan, capecitabin, perifosin). These results may be helpful for short-term therapy monitoring. In particular, antiangiogenic effects may be assessed more accurately by dPET-CT and FDG based on the calculation of the changes of k_1, additionally to the changes in the global SUV. Furthermore, antiproliferative effects may be evaluated based on the changes of k_3 and SUV. Short-term dPET-CT studies, e.g. prior therapy and after one or two chemotherapeutic cycles help to indentify resistant lesions and are crucial for the individualization and optimization of therapy, which is the goal of personalized medicine.

Conclusions

The data demonstrate, that FDG tracer activity over time, as measured by k_1 and k_3, is dependent on both the facilitated glucose transporter activities and the activities of the hexokinases. In particular, k_1 and k_3 of the applied 2-tissue-

compartment model are in compliance with the gene expression data. Furthermore, the 2-tissue compartment model is an accurate approach to obtain indirect information about the expression of glucose transporters and hexokinases.

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