Cardiac FAPI-PET-CT Imaging in Metastatic Cancer: A new approach to chemotherapy related cardiac fibrosis

HEIDELBERG UNIVERSITY HOSPITAL

Finn Reinhardt[1,2], Markus B. Heckmann[1,2], Daniel Finke[1,2], Uwe Haberkorn[4], Hugo A. Katus[1,2], Florian Leuschner[1,2], Lorenz H. Lehmann[1,2,3]

1 Department of Cardiology, Angiology, and Pneumology, Heidelberg University Hospital, Heidelberg, Germany | 2 German Centre for Cardiovascular Research (DZHK), Heidelberg/Mannheim partner site, Germany
3 Deutsches Krebsforschungszentrum (DKFZ) | 4 Department of Radiology, Nuclear Medicine, Heidelberg University Hospital, Heidelberg, Germany

Background

Fibroblast activation protein (FAP) plays an important role in extracellular matrix degradation as well as fibrosis and inflammation as well as cancer growth. It is listed as a hot candidate for targeted oncotherapy. TGFβ1 induced FAP expression is also crucial for cardiac wound healing and remodeling. While the assessment modality and quality of left ventricular systolic function and the coronary arteries is ever increasing, cardiac remodeling still lacks a reliable imaging modality in patients. In 2018, Lindner et. al. developed a tracer for positron emission scans targeting FAP. The tracer consists of a quinoline-based fibroblast activation protein inhibitor (FAPI) labeled with a radio nuclide. Aim of our study was to evaluate its potential in the detection of cardiovascular disease as FAPI excellently stains active fibrous tissue and inflammatory processes.

Methods

We retrospectively analyzed PET-CT scans from 230 patients suffering from different tumor entities presenting in our nuclear medicine department between 2017 and 2019. We correlated signal intensity and distribution pattern using multivariate logistic regression models applying Akaikes information criterion for model optimization. The scans were performed according to a standard protocol. 350 to 370mBq of Ga68 labeled FAPI were administered intravenously 60 minutes before the examination. A low dose whole body CT was used for attenuation correction and image fusion. A 3-D emission scan was subsequently performed. Standardized uptake values (SUVs) were calculated and reported in the following regions of interest: free left ventricular wall, aorta, gluteus muscle, liver and brain. In addition, all 17 segments of the left ventricle were measured. Patient characteristics included age, sex, cancer entity, body mass index, glomerular filtration rate, thyroid stimulating hormone, cardiovascular risk factors, diabetes mellitus, arterial hypertension, known coronary artery disease, known atrial fibrillation, previous radiation to the chest, chemotherapy (anthracyclines, platin derivatives, alkylating agents, antimetabolites, taxanes, topoisomerase inhibitors), checkpoint inhibitor use, FAPI signal pattern and cardiac medication. Statistical analyses were performed using R version 3.4.4 with the help of MASS and ggplot2 packages. Graphs were built in R version 3.4.4 with inhouse scripting using the shape and RColorBrewer.

Results

Patient characteristics	Cohort 1 N=185	Cohort 2 N=45	
FAPI SUV left ventricle	0.98 (IQR: 0.55)	0.87 (IQR: 0.39)	
FAPI pattern left ventricle			
. focal	42	8	
. diffuse	61	21	
. homogen	82	16	
FAPI SUV Aorta	1.14 (IQR 0.47)	1.24 (IQR 0.30)	
FAPI SUV brain	0.08 (IQR 0.07)	0.07 (IQR 0.06)	
FAPI SUV liver	0.86 (IQR 0.5)	0.85 (IQR 0.30)	
FAPI SUV Gluteus	1.00 (IQR 0.33)	1.02 (IQR 0.30)	
sex	male: 119 female: 59	male: 31 female14	
age	64.17 (IQR 16.62)	65.49 (IQR 20.31)	years
BMI	24.15 (IQR 4.72)	25.82 (IQR 4.79)	kg/m²
TSH	1.23 (IQR 1.19)	1.08 (IQR 0.92)	mU/l
Krea	65 (IQR 27)	71.00 (IQR 33)	µmol/l
urea nitrogen	5.34 (IQR 2.84)	5.34 (IQR 2.34)	mmol/l
C-reactive protein	10.6 (IQR 23.2)	28.65 (IQR 37.1)	mg/l
previous radiation to the chest	21 of 185	2 of 45	
coronary artery disease	27 of 185	4 of 45	
heart failure	2 of 185	0 of 45	
arterial hypertension	60 of 185	15 of 45	
atrial fibrillation	14 of 185	2 of 45	
diabetes mellitus type 2	24 of 185	5 of 45	
active smoker	24 of 185	7 of 45	
cardiac medication			
. ARB/ACEi	41 of 185	6 of 45	
. betablocker	27 of 185	5 of 45	
. statines	21 of 185	3 of 45	
. daily aspirin	27 of 185	5 of 45	
cancer entities			
. pancreatic carcinoma	43 of 185	1 of 45	
. bronchial carcinoma	20 of 185	3 of 45	
. colorectal carcinoma	16 of 185	2 of 45	
. oropharyngeal carcinoma	13 of 185	2 of 45	
. esophageal / gastric carcinoma	11 of 185	2 of 45	
. prostate carcinoma	11 of 185	3 of 45	
. ovarian carcinoma	10 of 185	1 of 45	
. other	59 of 185	31 of 45	
previous CTx			
. anthracyclines	28 of 185	4 of 45	
. antibodies	26 of 185	2 of 45	
. anti-metabolites	92 of 185	8 of 45	
. platin derivatives	92 of 185	8 of 45	
. alkylating agents	23 of 185	4 of 45	
. topoisomerase inhibitors	39 of 185	0 of 45	
. checkpoint inhibitors	21 of 185	2 of 45	

Table 1: Patient characteristics

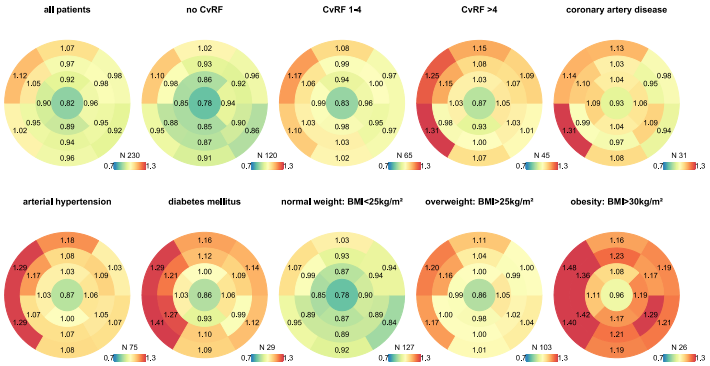

Figure 1: Bullseye 17 segment analysis of different subgroups with cardiovascular risk factors
The median signal intensity of the corresponding segment is displayed for each group. The number of patients in a group are seen in the right lower corner of each bullseye above the color scale. The color coding was taken from a spectral color scale consisting of 1000 distinct colors ranging from 0.7 (blue) to 1.3 (red) with 1.0 (yellow) being the center. Signal intensity was generally increased in the septal basal segments. This effect was most pronounced in arterial hypertension. Diabetes, arterial hypertension and obesity, which are all risk factors associated with metabolic stress and cardiac remodelling, show the highest increase in fibroblast activation protein inhibitor (FAPI) signals.

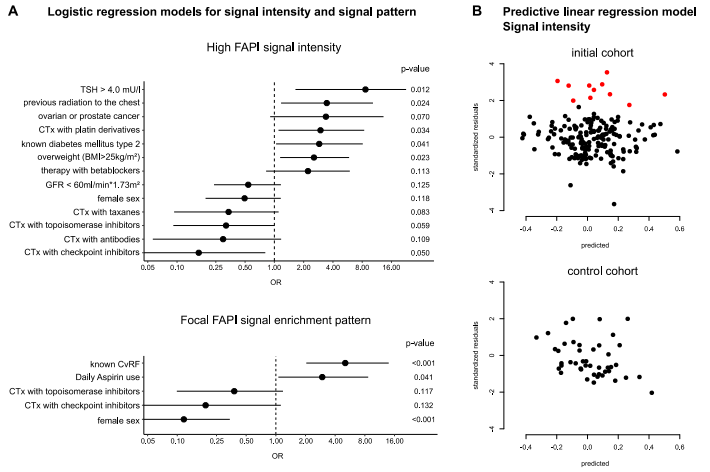

Figure 2: Multivariate logistic regression and linear prediction model for fibroblast activation protein inhibitor signal in the myocardium
(A) Multivariate logistic regression models for signal intensity and focal enrichment. Odds ratios (OR) are depicted as a dot. Lines mark the 95% confidence interval. While metabolic variables, such as increased TSH, radiation, diabetes, overweight and different chemotherapies, are associated with an increased fibroblast activation protein inhibitor (FAPI) signal, focal FAPI enrichment patterns are mainly associated with cardiovascular risk. N=185 for both analyses.
(B) Linear regression model for FAPI signal intensity prediction and outlier analysis based on significant variables of the multivariate logistic regression analysis. The model was established with the initial cohort (N=185) and tested for accuracy with a control cohort (N=45). Outliers are marked in red in both plots. Outliers were defined as patients with residuals (actual – predicted FAPI signal) above the 95% mark of the initial cohort.

Conclusion

- FAPI-PET-CT scans represent a new imaging modality to display active cardiac remodeling.
- High signal intensities are associated with cardiovascular and metabolic disease especially arterial hypertension, diabetes and obesity.
- A focal enrichment pattern is highly suggestive for an underlying cardiovascular disease.

Disclosures

Finn Reinhardt has no conflict of interest to declare.

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