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IMAGING VIGNETTE

FAPI PET Imaging Supports Clinical Decision Making in Academic Cardiology Practice

A Pictorial Imaging Vignette

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Advances in nuclear cardiology molecular imaging improve decision making in clinical cardiology. Fibroblast activation protein alpha (FAP) is a homodimeric membrane-bound serine protease with intracellular and extracellular soluble forms. Positron emission tomography (PET) imaging using radiolabeled fibroblast activation protein alpha inhibitors (FAPIs) has emerged as a promising molecular imaging tool for oncology but also cardiology, possibly providing new insights into the pathophysiology of diseases. FAP is specifically expressed by early-stage activated fibroblasts during wound healing and cardiac remodeling. Therefore, FAPI PET provides a unique opportunity to visualize and quantify cardiac fibrosis, a key pathophysiological process involved in several cardiovascular diseases. Hence, this imaging modality is a powerful tool that can aid in clinical decision making. The complete potential of FAPI PET in nuclear cardiology has not been recognized fully to date. The purpose of this pictorial imaging vignette is to demonstrate potential applications of this modality in understanding the pathophysiologic aspects of common and rare myocardial diseases.

STRUCTURE OF IMAGING VIGNETTE

PET/computed tomography (CT) or PET/magnetic resonance imaging (MRI) was performed using ^{68}Ga-labeled FAPI-46 ([^{68}Ga]Ga-FAPI-46) according to our established imaging protocols (administered activities and imaging delays are provided in Figures 1 to 10). Images are presented from top to bottom clockwise (when applicable) as follows: [^{68}Ga]Ga-FAPI-46 PET maximum-intensity projection (anterior view), myocardial 3-dimensional rendering, bull's-eye representation, and multiplanar reconstructions (transversal and sagittal view); CT/MRI transversal and sagittal view; PET/CT or PET/MRI fusion transversal and sagittal view; and echocardiography parasternal long axis and apical 4-chamber view. If available, other patient-specific molecular imaging modalities are supplemented.

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ABBREVIATIONS AND ACRONYMS

CT = computed tomography

FAP = fibroblast activation protein alpha

FAPI = fibroblast activation protein alpha inhibitor

MRI = magnetic resonance imaging

PET = positron emission tomography

CONCLUSIONS

FAPI PET proved to be of clinical benefit in myocardial disease, including rare cases. FAP expression may be an indicator for cardiac involvement in various systemic diseases, and additional imaging features may be derived from PET/MRI. Repeated FAPI PET can be used for treatment monitoring. Further studies are needed to analyze prognostic value and enable applications in therapeutic decisions.

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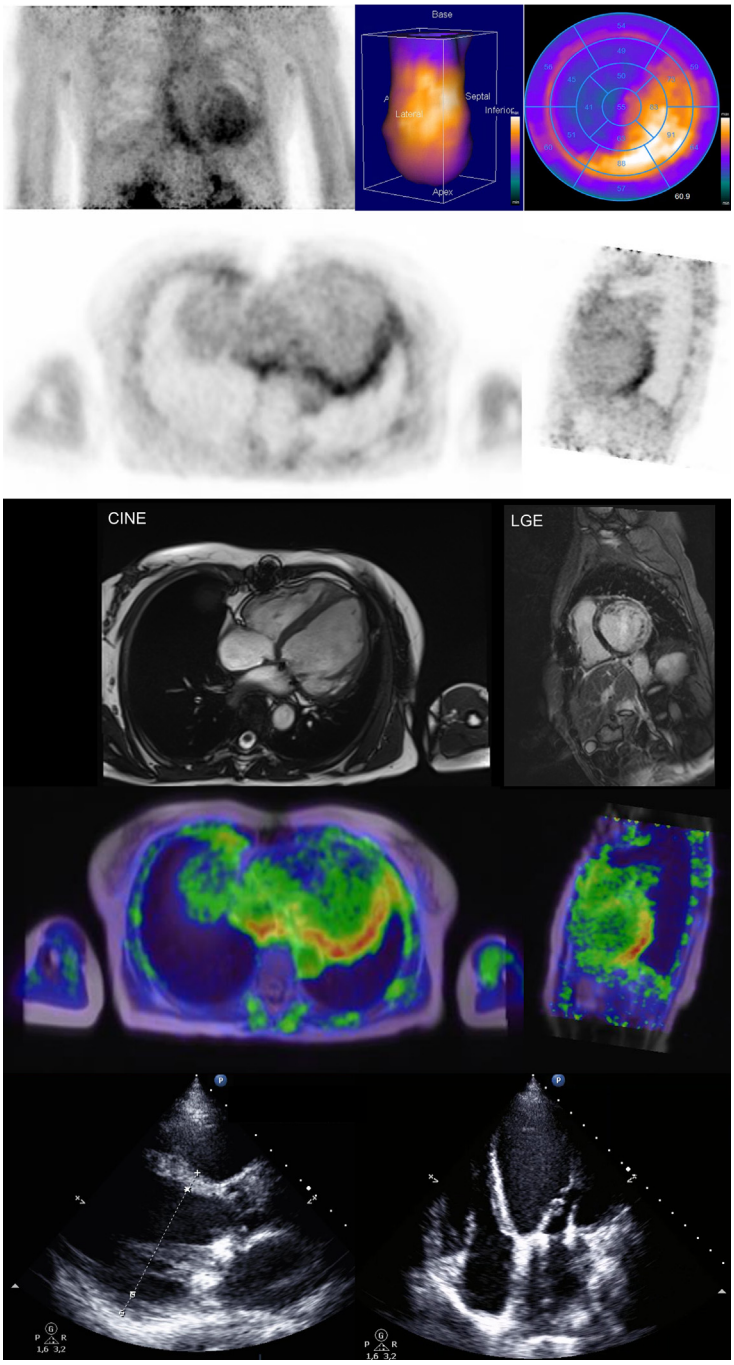
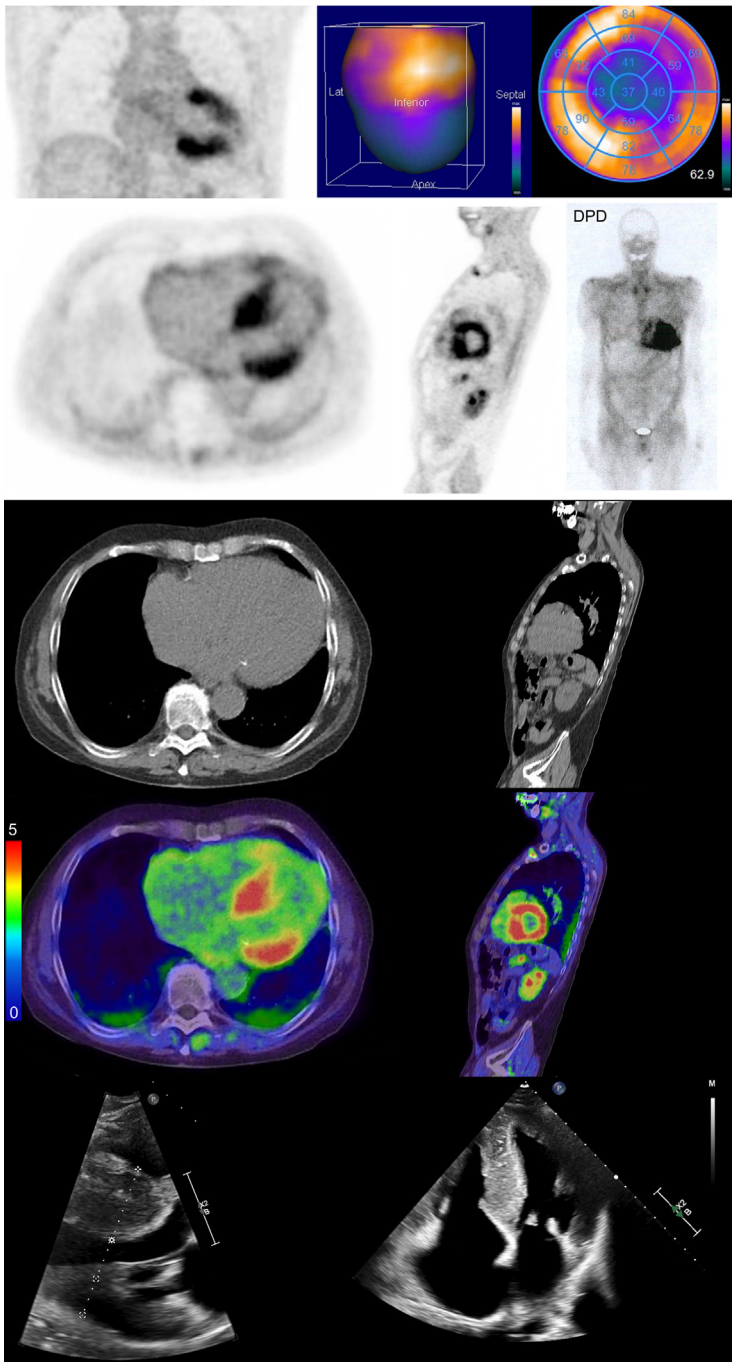
FIGURE 1 **Chagas Cardiomyopathy**



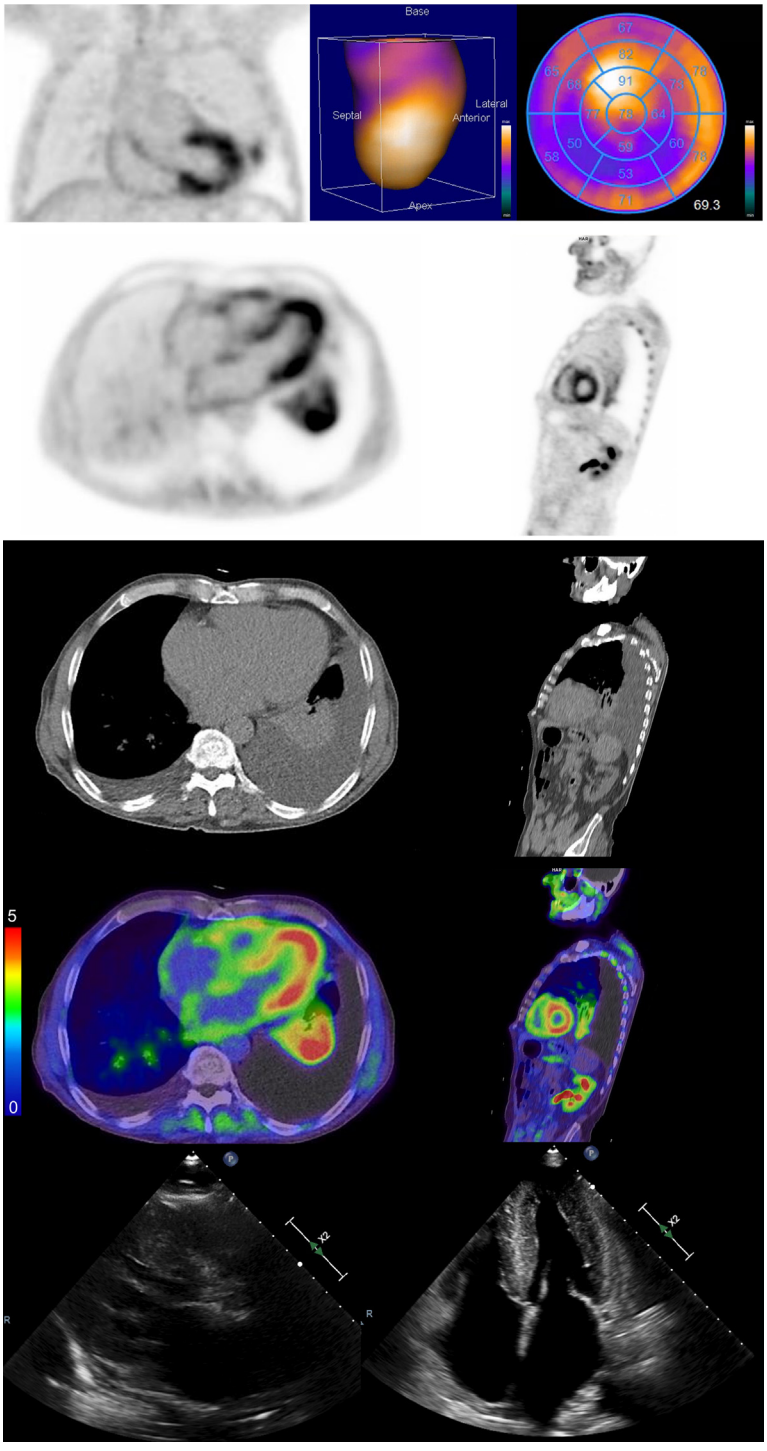
A 61-year-old female patient with a long history of untreated Chagas cardiomyopathy and mitral valve reconstruction. The patient suffers from chronic heart failure with mildly reduced ejection fraction and a dilated left ventricle. PET/MRI was performed using 100 MBq [^{68}Ga]Ga-FAPI-46 (acquisition 68 minutes postinjection). Intense inferolateral focal fibroblast activation protein alpha inhibitor (FAPI) accumulation was detected in the myocardium. Caused by the protozoan parasite *Trypanosoma cruzi*, Chagas cardiomyopathy is common in Latin America.[1] Chronic myocarditis and myocytolysis with reparative fibrosis are the hallmark of Chagas cardiomyopathy leading to chronic heart failure approximately 2 decades after the initial infection.[2] The results from FAPI PET show that fibrotic processes are still active years after the original infection, indicating that antifibrotic treatment may represent a relevant therapy. FAPI PET may help to assess the prognosis and therapeutic response, serving as a noninvasive biomarker to quantify active myocardial fibrosis in vivo. FAPI = fibroblast activation protein alpha inhibitor; MRI = magnetic resonance imaging; PET = positron emission tomography.

FIGURE 2 Wildtype Transthyretin Amyloidosis



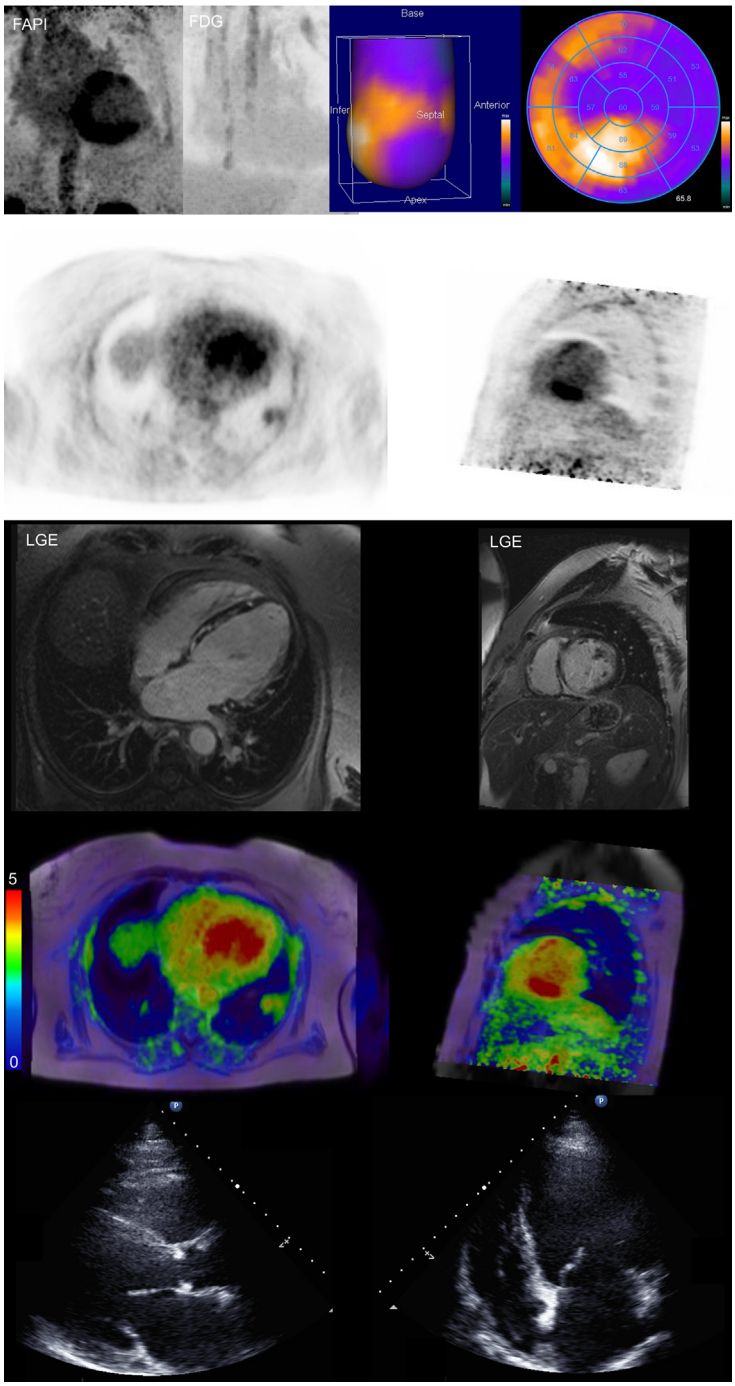
A 79-year-old male patient with chronic heart failure caused by wildtype transthyretin amyloidosis (wtATTR). Cardiac wtATTR is an infiltrative myocardial disease in which extracellular deposits of misfolded mono- or oligomers of serum transthyretin (TTR) evoke a progressive amyloid cardiomyopathy,[3] which may lead to extensive myocardial fibrosis.[4] At the time of PET imaging, the patient had been treated with the TTR stabilizer tafamidis for 36 months. FAPI PET/CT images (administered activity: 109 MBq [^{68}Ga]Ga-FAPI-46, imaging delay: 16 minutes) show intense basal cardiac tracer uptake, indicating fibrotic activity. Echocardiography showed preserved ejection fraction, severe ventricular hypertrophy, and high-grade diastolic dysfunction. Scintigraphy with the bone-avid tracer [^{99m}Tc]Tc-3,3-diphosphono-1,2-prop-anodicarboxylic acid (DPD) shows strong cardiac uptake which is typical for this disease. Bull's-eye representation of FAPI uptake corresponds with apical preserved contraction as in strain analysis. In the absence of pretreatment scans, no data regarding the fibrosis-modifying effect can be shown. Nevertheless, FAPI PET may play an important role in the assessment of disease burden and may be used to monitor treatment response. CT = computed tomography; other abbreviations as in Figure 1.

FIGURE 3 **Light-Chain Amyloidosis**



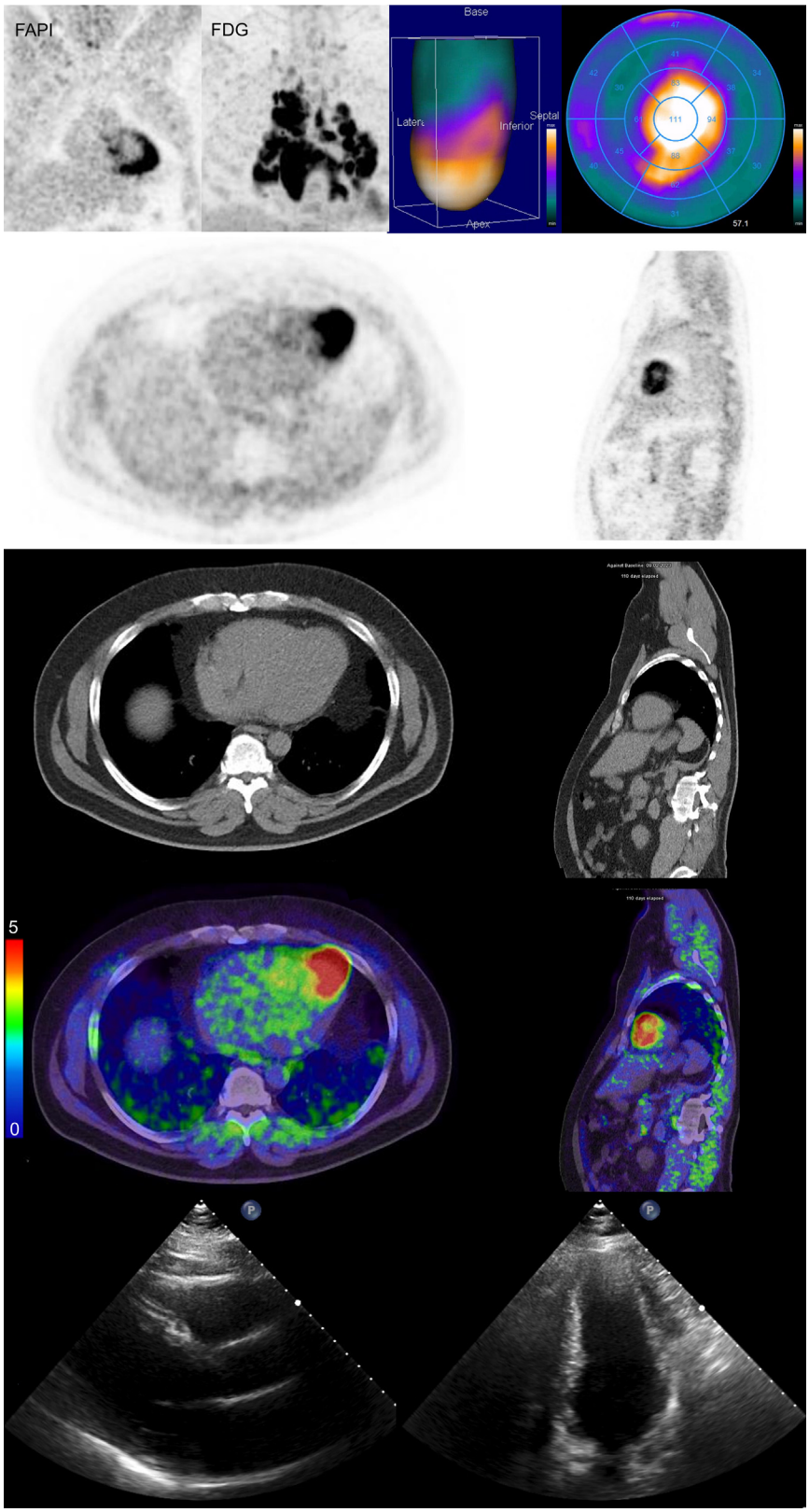
The second most prevalent form of amyloidosis is light-chain (AL) amyloidosis. A 79-year-old male patient with heart failure caused by AL amyloidosis showed intense myocardial FAPI uptake, which is, in contrast to wtATTR, distributed in a ubiquitous pattern. PET/CT was acquired 29 minutes after the injection of 152 MBq [^{68}Ga]Ga-FAPI-46. Echocardiography showed a hypertrophic ventricle with diastolic dysfunction and basal hypokinesis with preserved apical contractility. As in wtATTR cardiomyopathy, myocardial fibrosis may be involved in the pathogenesis of myocardial dysfunction in AL amyloidosis.[4] Therefore, FAPI PET visualizing active fibrotic remodeling may play a role in assessing therapeutic effects in cardiac AL amyloidosis. In contrast to cardiac ATTR amyloidosis, patients with cardiac AL amyloidosis are typically negative in scintigraphy with bone-avid tracers like DPD. Abbreviations as in **Figures 1 and 2**.

FIGURE 4 **Cardiac Sarcoidosis**



A 59-year-old female patient with a history of pulmonary sarcoidosis. As chronic inflammatory disease, sarcoidosis leads to permanent fibrosis and end-organ damage, primarily in the lungs, but can also affect the heart.[5] Typically, ^{18}F-fluorodeoxyglucose (FGD) PET showing increased glycolysis in active inflammation is used for in vivo assessment of cardiac involvement. When FGD PET is negative, FAPI PET can be used to assess for myocardial fibrosis, which occurs in 5% to 10% of cases and is a valuable diagnostic tool as echocardiographic parameters remain equivocal. Moreover, FAPI PET has a potential role in guiding immunomodulatory therapy.[6] In this case, FDG PET was negative, but FAPI PET/MRI using 103 MBq [^{68}Ga]Ga-FAPI-46 (dynamic acquisition for 60 minutes) showed intense fibrotic activity in the basal septum and inferior wall of the left ventricle. Transthoracic echocardiography showed reduced left ventricular ejection fraction, diastolic dysfunction grade II, and moderate septal thinning. Abbreviations as in Figure 1.

FIGURE 5 Cardiac Sarcoidosis and Hypertrophic Cardiomyopathy



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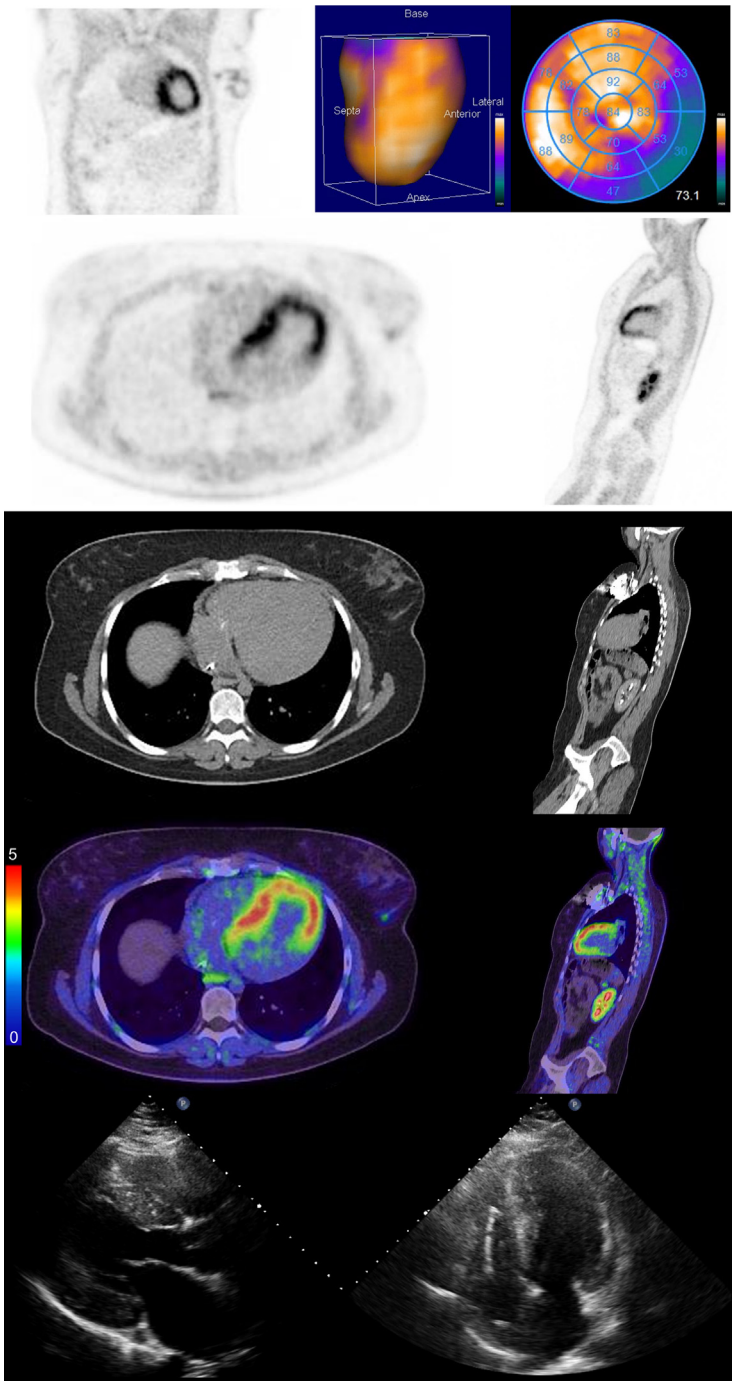
KEY WORDS FAPI PET, fibrosis imaging, nuclear cardiology

FIGURE 5 Continued

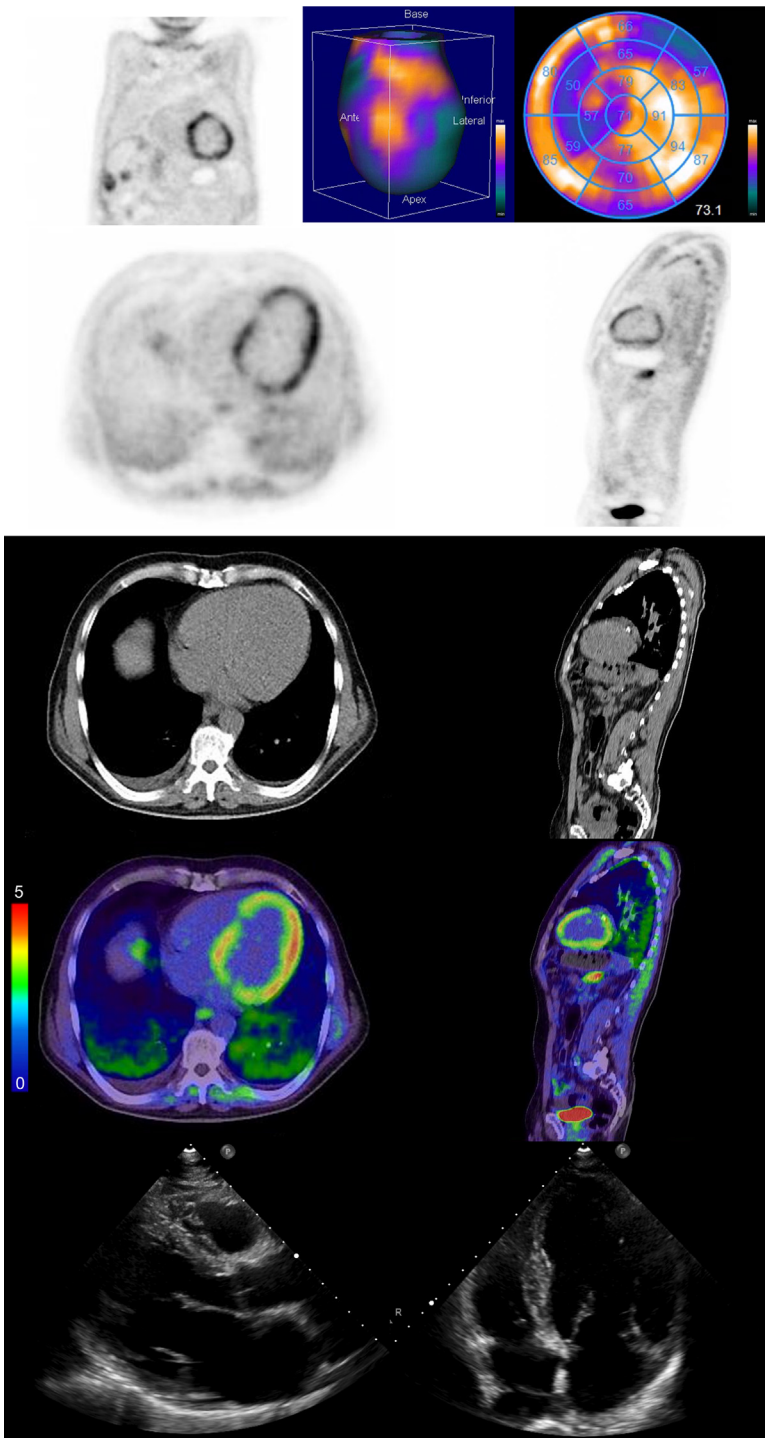
Images of a 46-year-old male patient with a history of hypertrophic cardiomyopathy and myectomy who presented with shortness of breath. Combination of FAPI PET/CT (administered activity: 103 MBq [^{68}Ga]Ga-FAPI-46, imaging delay: 10 minutes) and FGD PET revealed additional underlying and later biopsy-proven pulmonary sarcoidosis and emphasis of fibroblast activation in the apical left ventricle with corresponding mildly increased glycolytic activity. Notably, 5 years after myectomy, no active fibroblasts were detected in the left ventricular outflow tract (LVOT). Echocardiography confirmed a reduction of LVOT muscle mass. In similar cases, a combination of FDG and FAPI PET imaging is a valuable tool to assess the cardiac involvement of the disease. The use of these 2 tracers can help to differentiate between the disease entities. Abbreviations as in Figures 1, 2, and 4.

FIGURE 6 **Chronic Lymphocytic Myocarditis in Hypertrophic Cardiomyopathy**



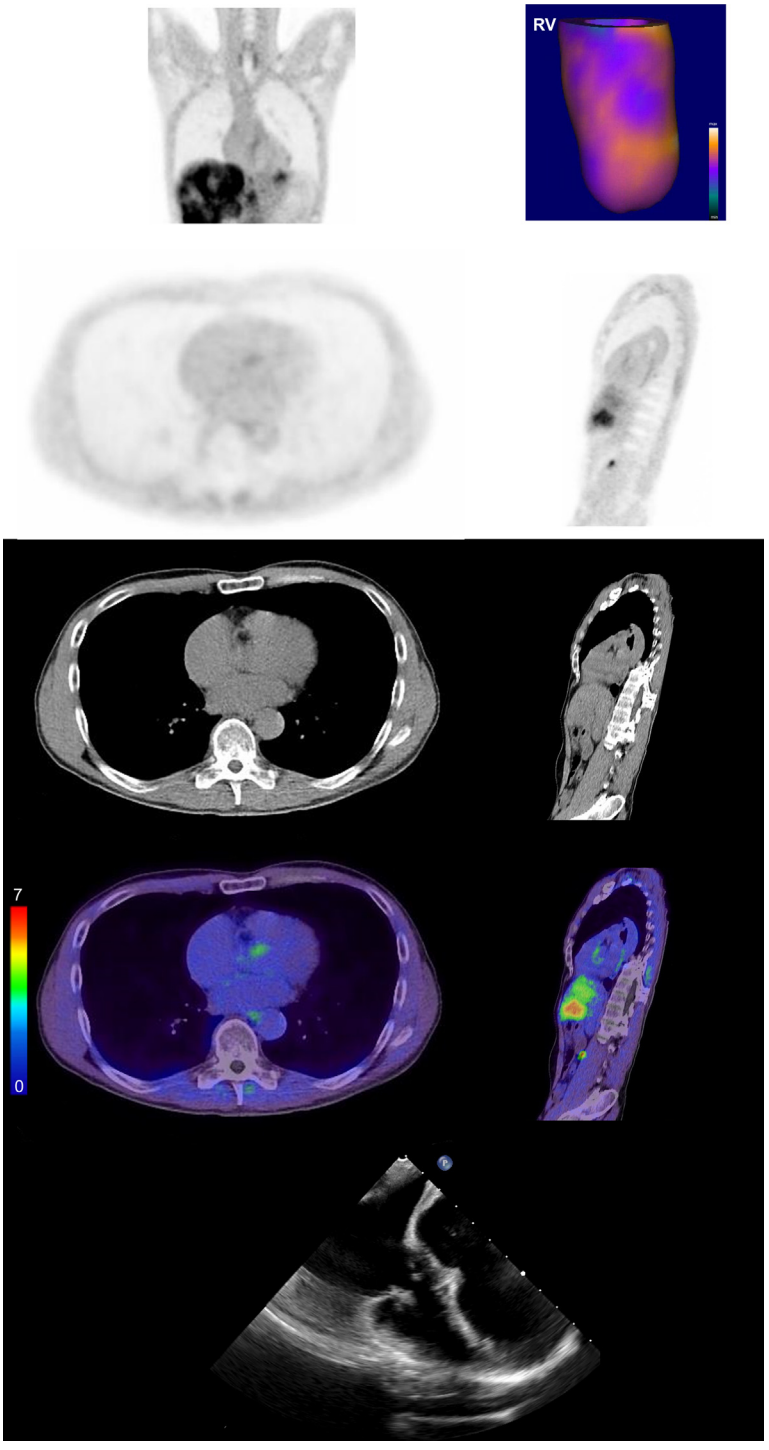
Hypertrophic obstructive cardiomyopathy (HOCM) is associated with increased morbidity. Myocardial fibrosis here contributes to disease progression and adverse cardiovascular events. Moreover, uptake in FAPI PET was described to be associated with the risk of sudden cardiac death in patients with hypertrophic cardiomyopathy and can detect more involved myocardium than cardiac MRI.[7,8] With new treatment options,[9] treatment monitoring will be of great interest. In this case, FAPI PET/CT was performed in a 24-year-old male patient with a history of HOCM, myectomy, and clinically suspected myocarditis (administered activity: 144 MBq [^{68}Ga]Ga-FAPI-46, imaging delay: 50 minutes). It showed intense FAPI uptake of the hypertrophic left ventricular muscle as a combined activity of a later biopsy-confirmed chronic lymphocytic myocarditis and persistence of parvovirus B19 and human herpesvirus 6. Transthoracic echocardiography showed a hypertrophic left ventricle after myectomy with mildly reduced left ventricular ejection fraction and diastolic dysfunction grade II. Abbreviations as in **Figures 1 and 2**.

FIGURE 7 Cancer Therapy-Related Cardiotoxicity



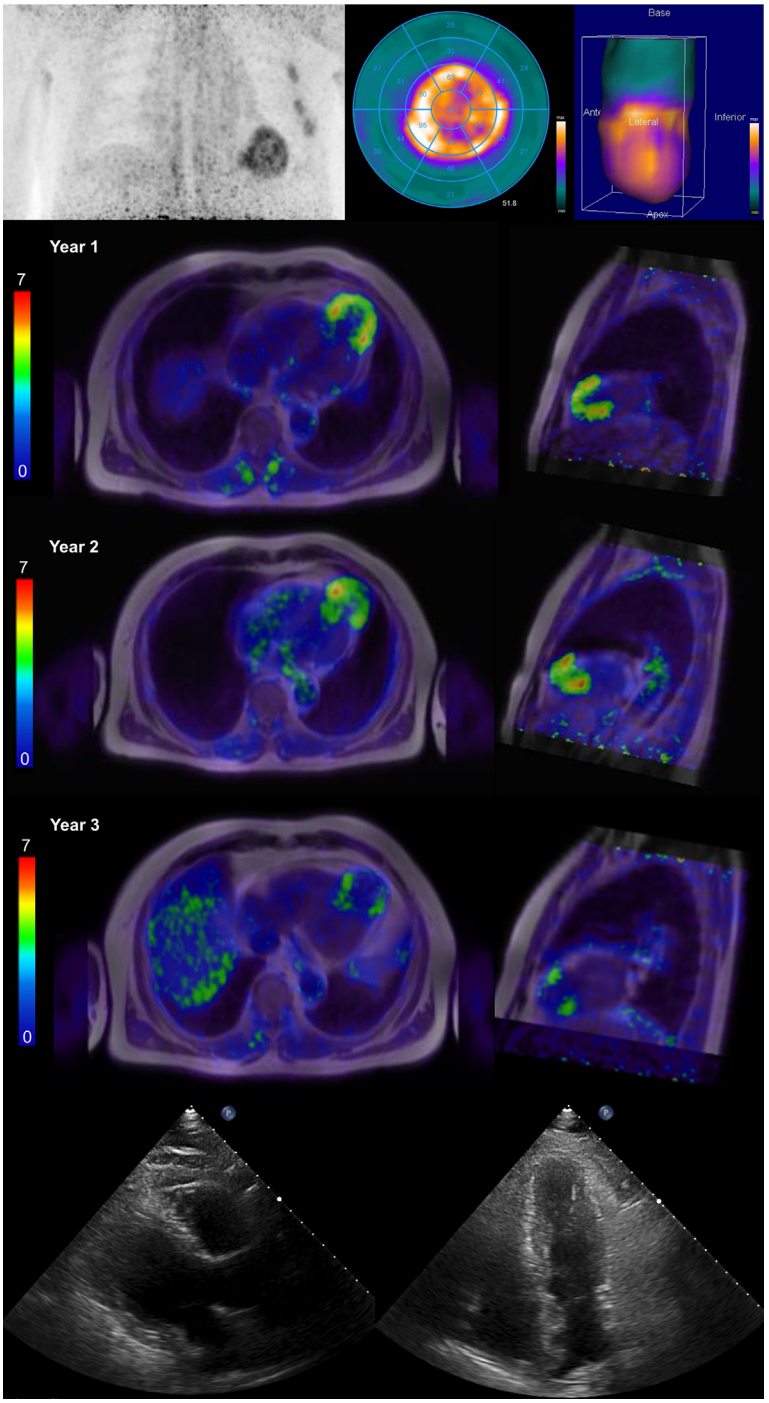
Cancer therapy-related cardiotoxicity is a feared side effect of antineoplastic treatment. Nuclear cardiology can help identify such cardiotoxicity.[10,11] Here, a 72-year-old male patient with metastatic ductal adenocarcinoma of the pancreas received systemic chemotherapy with irinotecan, oxaliplatin, calcium folinate, and fluorouracil. During the restaging process, the patient underwent [^{68}Ga]Ga-FAPI-46 PET/CT (administered activity: 144 MBq, imaging delay: 14 minutes) while under cardiac deterioration in which cardiac fibroblast activation protein alpha (FAP) expression was detected. Cardio-oncology consultation with transthoracic echocardiography showed acute cardiotoxicity with reduced left ventricular ejection fraction (40%) and reduced global longitudinal strain (−12%). In the future, uptake in FAPI PET may be a potential molecular imaging biomarker of early cardiac damage in patients under cytotoxic immune therapy and chemotherapy,[12] which could be used for monitoring of patients before, during, and after treatment. Abbreviations as in Figures 1 and 2.

FIGURE 8 Carcinoid Heart Disease



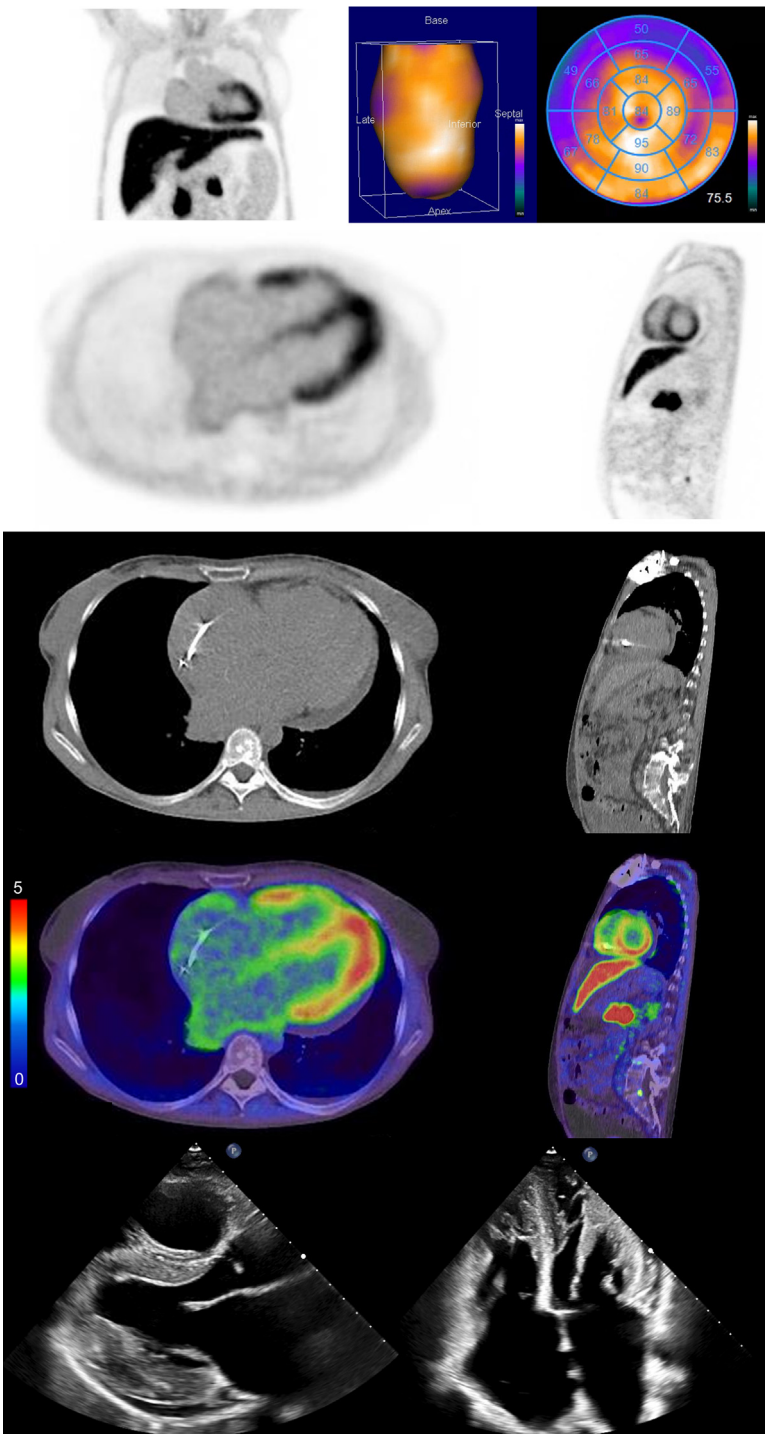
Neuroendocrine tumors can cause carcinoid heart disease or Hedinger syndrome, a rare disease developed in patients with an advanced tumor state that primarily leads to fibrosis of the tricuspid valve, resulting in tricuspid stenosis. Patients have a poor long-term prognosis.[13] Combined noninvasive and functional imaging is a key tool in the assessment of disease severity. A 54-year-old male patient underwent FAPI PET acquisition using 115 MBq [^{68}Ga]Ga-FAPI-46 13 minutes after injection that showed discreet circular tracer uptake in the tricuspid valve anulus. Here, 3-dimensional rendering is a display of the right ventricle. Transesophageal echocardiography showed a thickened tricuspid valve (mean pressure gradient 7 mm Hg). FAPI PET has not been evaluated for the diagnosis of carcinoid heart disease yet, but early data[14] and our data support its potential utility as an imaging biomarker. Additional studies are imperative because an early diagnosis could potentially impact patient prognosis. Abbreviations as in Figure 1.

FIGURE 9 Ischemic Heart Disease



A 65-year-old patient with a history of ST-elevation myocardial infarction and apical aneurysm. FAPI PET/MRI was performed once a year for 3 times after the initial event (ie, 62 minutes, 10 minutes, and 10 minutes after the administration of 92 MBq, 170 MBq, and 176 MBq of [^{68}Ga]Ga-FAPI-46, respectively). Here, the initial imaging is presented showing intense FAPI uptake in the apex of the left ventricle. Interestingly, FAPI uptake was still visible in the follow-up imaging 3 years after the initial event, suggesting that antifibrotic therapy is important in postinfarct patients. In the published reports, FAPI PET was described to be suitable for monitoring of left ventricular remodeling.[15,16] In contrast to preclinical data,[17] the focal FAP signal is still visible in this patient years after myocardial infarction. Transthoracic echocardiography showed mildly reduced left ventricular function with akinetic apical aneurysm. Abbreviations as in **Figures 1 and 7**.

FIGURE 10 **Ciliopathy**



A 54-year-old female patient with Tubby-like protein (TULP) 3-sequence variant ciliopathy resulting in organ fibrosis causing terminal heart, liver, and kidney failure.[18] To our knowledge, this is the first time a TULP3 sequence variant ciliopathy has been investigated using FAPI PET. PET/CT was performed using 115 MBq [^{68}Ga]Ga-FAPI-46 13 minutes postinjection. Intense ubiquitous focal FAP expression was detected. Histopathology revealed patchy myocardial fibrosis with replacement fibrosis. Echocardiography showed hypertrophic myocardium with highly reduced left ventricular ejection fraction. This case shows that FAPI PET is a feasible methodology for exploring cardiac fibrosis in ciliopathies. Abbreviations as in **Figures 1, 2, and 7**.