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REVIEW

^{68}Ga-FAPi: Pathways and Diagnosis in Cardiac Imaging

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Abstract

Purpose of Review Myocardial fibrosis is a response to myocardial injury and plays a pivotal role in ventricular remodeling. Different patterns of fibrosis are associated with different disease states, but the presence and amount of fibrosis provide a different impact on prognosis.

Recent Findings In the latest years, fibroblast activation protein inhibitor (FAPi) positron emission tomography (PET) gain interest for its potential in detecting myocardial fibrosis, in differentiating between active and chronic disease, and in the assessment of disease progression and response to treatment.

Summary We aim to highlight the most relevant current applications of FAPi PET/CT in cardiovascular imaging, focusing on its applications, advantages, limitations, and to underline future clinical perspective.

Keywords ^{68}Ga-FAPi-04 · FAPi · Fibroblast Activation Protein · Myocardial Fibrosis · Myocardial Infarction · Positron Emission Tomography/Computed Tomography (PET/CT)

Introduction

^{68}Ga-labeled fibroblast activation protein (FAP) inhibitor (FAPi) is a positron emission tomography (PET) tracer, whose use has been consistently increasing in recent years, especially in the oncological field [1]. This tracer targets a membrane-anchored peptidase (FAP) with dipeptidyl peptidase, endopeptidase, and gelatinase activity related to fibroblast activation [1, 2].

FAP is expressed by myofibroblasts, a subpopulation of fibroblasts with contraction properties similar to smooth muscles, that are a part of the tumor microenvironment (TME) in the extracellular matrix (ECM), together with blood vessels, growth factors and cytokines [3•]. These favorable characteristics render ^{68}Ga-FAPi imaging suitable to assess the presence and the metastatic involvement of various cancers [4–6].

More recently, the use of ^{68}Ga-FAPi has been investigated also in cardiovascular imaging [7], based on the demonstration of FAP overexpression in inflamed tissues [8]. In the heart, an initial inflammation with subsequent fibroblast activation [9] is followed by a reparative process, characterized by fibroblast proliferation and differentiation in myofibroblast, resulting in ECM deposition and apoptosis of the granulation tissue [10]. It is important to note that timing and physiologic balance between inflammatory and reparative processes are key elements to guarantee proper healing [11] and their dysregulation plays a pivotal role in almost all form of myocardial disease, by worsening tissue damage therefore increasing the probability of adverse outcome [12].

The aim of the present paper is to review the current applications of FAPi PET computer tomography (FAPi PET/CT) in cardiovascular imaging, focusing on its applications, advantages, limitations, and future perspectives in the context of clinical indication.

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Materials and Methods

A comprehensive computer literature search strategy using PubMed databases was carried out looking for articles on the applications of FAPi in cardiovascular imaging. The string used for the search included a combination of the terms: "FAP" or "FAPi" or "fibroblast activation protein" or "myocardial fibrosis" or "myocardial infarction" and "cardiac PET" or "cardiac positron emission tomography." The search was updated to May 2023, taking into consideration both clinical and preclinical studies published in English that used FAP-specific PET in cardiovascular field. The references of the retrieved articles were also checked as not to miss important clinical studies. Review articles, articles not in the field of interest, and commentaries were excluded. Papers on future perspectives in the field and experimental data were also considered eligible.

Three researchers (CEP, PF, and IG) independently reviewed the titles and the abstracts of the retrieved literature, selecting relevant articles according to the inclusion criteria mentioned above. Disagreements were resolved in a consensus meeting.

Results

Applying the search terms, 44 articles were retrieved. Titles and abstracts were carefully checked. Of all the articles, we identify 30 articles meeting the inclusion criteria. More specifically, 24 articles were related to clinical studies including 11 case report, 2 articles were translational studies, and 4 articles were preclinical studies. An overview of published articles and case reports on cardiac FAPi PET imaging is summarized in Table 1.

Correlation with Cardiovascular Risk Factors

In the largest retrospective analysis to date, Heckmann and colleagues [13••] investigated the correlation between myocardial FAPi-uptake in 229 patients undergoing ^{68}Ga-FAPi PET/CT scan during oncologic follow-up. In their study, increased ^{68}Ga-FAPi uptake correlated well with established cardiovascular risk factors (i.e., overweight and type II diabetes mellitus) but not with coronary artery disease (CAD) or prior myocardial infarction (MI). In addition, increased FAPi uptake was associated with reduced left ventricular ejection fraction (LVEF) in a sub-group of 44 patients. Similar findings were reported by Siebermair et al., wherein FAPi uptake correlated with age and LVEF [7]. Finally, also a retrospective study with a small cohort found a relationship between myocardial FAPi uptake, age, and high blood glucose levels [14•]. Given the retrospective nature of these studies, no firm conclusions can be drawn. Nevertheless, they support the concept of the interconnection between fibroblast activation and cardiac disease, thus suggesting a potential factor involved in their progression.

Coronary Artery Disease

Several reports also exist on FAPi imaging in patients with acute myocardial infarction (AMI). Back in 2015, Tillmanns et al. [40] investigated in a rat model the expression of FAP in activated fibroblasts after AMI. From this preclinical study, it seems that FAP expression follows a dynamic timecourse, with highest activity in the first week after AMI, especially in the peri-infarct area. These findings were confirmed by Varasteh et al. [15], wherein a peak in ^{68}Ga-FAPi uptake was detected at day 6 post-AMI in rats, mainly in the ischemic borderzone, while FAP expression returned to near baseline by 2 weeks. Conversely, in another preclinical FAPi imaging study with ^{68}Ga-MHLL1, persistent FAP expression was seen in the infarct relative to the non-infarcted remote myocardium between 7 and 21 days after AMI, suggesting a more stable expression over time compared to the previous 2 studies [16].

The possibility to reveal areas of inflamed myocardium after AMI has been confirmed in subsequent clinical studies. Both Xie et al. [17••] and Diekmann et al. [18••] showed in their work increased ^{68}Ga-FAPi uptake after AMI. In both papers, patients exhibited intense ^{68}Ga-FAPi uptake in the infarct zone, exceeding the perfusion defect identified either by nuclear perfusion imaging or cardiac magnetic resonance (CMR) late gadolinium enhancement (LGE) (Fig. 1), also consistent with previous case reports [18••, 19].

Following these observations, FAPi PET imaging has been directed toward the identification of early signs of ventricular remodeling post-AMI. In this regard, it was shown that FAPi uptake well correlates to signs of myocardial injury including reduced LVEF and peak creatinine kinase levels [20•]. Hence, it is conceivable that the amount of activated fibroblasts in the infarcted and non-infarcted myocardium directly affects subsequent remodeling.

Consistent with this concept, a recent study [21] suggested that FAPi PET can noninvasively monitor the activated fibroblasts early after AMI, which are ultimately responsible for the occurrence of reparative fibrosis. Also, Zhang et al. [41••] showed that the FAPi uptake of injured myocardium as detected early after AMI has a predictive value for late LV remodeling at 12-month follow-up. This prognostic value probably pertains to the observation that a long persistence of activated myocardial fibroblasts is

Table 1 Summary of studies on current applications of FAP-specific PET/CT in cardiovascular field

Authors/journal	Study design	Tracer	Conclusion and relevance
Correlation with cardiovascular risk factors			
Heckmann MB et al. [13••], Circ. Cardiovascular Imaging 2020	Clinical	^{68}Ga-FAPI	High cardiac FAP signal correlate with cardiovascular risk factors and metabolic disease
Siebermair J et al. [7], J Nucl Cardiol 2020	Clinical	^{68}Ga-FAPI-04	Higher age, a history of CAD/MI and an impaired LVEF are associated with increased localized FAP uptake
Lyu Z et al. [14•], Front Cardiovasc Med 2022	Clinical	Al^{18}F-NOTA-FAPI-04	High FAPI uptakes correlate with cardiovascular risk factors and the distribution of coronary plaques
Coronary artery disease			
Varasteh Z et al. [15], J Nucl Med 2019	Preclinical	^{68}Ga-FAPI-04	Peak tracer uptake at day 6 post-MI in rats after coronary artery injury, mainly in the border-ischemic area, returning to near baseline by 2 weeks
Langer LBN et al. [16], Theranostics 2021	Preclinical	^{68}Ga- MHLL1	At 7 days after coronary artery ligation, elevated FAPi uptake in the infarct and border zone, persisted to 21 days. Autoradiography and histology confirmed regional tracer uptake in the infarct and border zone regions. Immunostaining delineated persistent FAP expression at 7 days and 21 days post-MI
Xie B et al. [17••], Eur J Nucl Med Mol Imaging 2022	Clinical	^{18}F-FAPI	FAPI imaging detects more involved myocardium than CMR in reperfused STEMI, and is associated with myocardial damage and follow-up LVEF
Diekmann J et al. [18••], J Am Coll Cardiol. 2021	Clinical	^{68}Ga-FAPI	Intense FAPI uptake in the infarct zone, exceeding the perfusion defect identified either by nuclear perfusion imaging or cardiac magnetic resonance (CMR) LGE
Notohamiprodjo S et al. [19], J Nucl Cardiol. 2022	Clinical	^{68}Ga-FAPI-04	The uptake of FAPI extends beyond the actual infarcted area and overestimates the infarct size as confirmed by follow-up CMR
Kessler L et al., [19], Clin Nucl Med. 2021	Clinical	^{68}Ga-FAPI	Intense FAPI uptake in the infarct and neighboring border zone. Correlation with biomarker- levels of myocardial injury including left ventricular function and peak creatine kinase level
Qiao P et al. [20•], Mol Pharm 2022	Preclinical	^{68}Ga-FAPI-04	FAPI can noninvasively monitor the activated fibroblasts in the early stage post-acute MI and may be helpful for evaluating the degree of reparative fibrosis
Zhang M et al. [21], Eur J Nucl Med Mol Imaging 2022	Clinical	^{68}Ga-DOTA-FAPI-04	Baseline FAPI uptake volume as detected early after AMI may have potential predictive value for late LV remodeling
Heart failure in non-ischemic disease			
Wang G et al. [22], Eur J Nucl Med Mol Imaging 2022	Preclinical	^{68}Ga-FAPI-04	Activated fibroblasts in the heart and liver after pressure overload were linked in an early fibrotic environment, able to predict the occurrence of HF
Song W et al. [23], Eur J Nucl Med Mol Imaging 2023	Translational	^{68}Ga-FAPI	As HF progresses, FAPI uptake is high in the early stages and then gradually decreases. Detection of early active FAP expression may assist treatment decision making in HF patients
Right ventricular imaging in pulmonary arterial hypertension			
Wang L et al. [24], J Nucl Cardiol. 2022	Clinical	^{68}Ga-FAPI-04	Significant FAPI uptake in the RV free wall and right atrium. RV insertion point presented with focal uptake. No uptake in the LV myocardium
Xing H-Q et al. [25], J Nucl Cardiol. 2022	Clinical	^{68}Ga-FAPI-04	Intense FAPI uptake in the myocardium of the free wall of RV and milder uptake in the insert point of RV. No uptake in the LV myocardium
Chen BX et al. [26], Eur J Nucl Med Mol Imaging. 2022	Clinical	^{68}Ga-FAPI-04	Tracer uptake mainly localized in the RV free wall. Enhanced fibroblast activation reflects the thickening of the RV wall and decreased RV contractile function

Table 1 (continued)

Authors/journal	Study design	Tracer	Conclusion and relevance
Gu Y et al. [27], J Nucl Cardiol. 2023	Clinical	^{68}Ga-FAPI	FAPI imaging is feasible to directly visualize fibrotic remodeling of RV in patients with PAH. Significant positive correlation between cardiac FAPI uptake and total pulmonary resistance and the level of N-terminal pro b-type natriuretic peptide
Chemotherapy-induced cardiotoxicity			
Niu N et al. [28], Eur Heart J Cardiovasc Imaging. 2022	Clinical	^{68}Ga-FAPI	Intense focal and heterogeneous FAPI uptake in the anterior, lateral, and septal wall but not into the inferior wall. Potential tool for the visualization of the pathophysiology of ICIs associated myocarditis beyond inflammation
Totzeck M et al. [29•], Eur Heart J. 2020	Clinical	^{68}Ga-FAPI	Intense FAPI uptake of the LV myocardium in patients with previous systemic antineoplastic therapies may reveal FAP activation due to cardiotoxicity
Wei Y et al. [30], Eur J Nucl Med Mol Imaging. 2023	Translational	Al^{18}F-NOTA-FAPI-04	FAPI-PET can detect radiation-induced myocardial damage before a decrease in LVEF, with evident implications for early monitoring of cardiac toxicity
Hypertrophic, dilatated, and hypertensive cardiomyopathy			
Wang L et al. [31], Radiology. 2023	Clinical	^{18}F-FAPI	Intense and heterogeneous FAPI activity in hypertrophic cardiomyopathy, associated with 5-year risk of sudden cardiac death
Shi X et al. [32], J Nucl Cardiol. 2022	Clinical	^{68}Ga-FAPI-04	In combination of CMR examinations for cardiomyopathy, FAPI imaging could provide early and supplemental information for characterizing dilated cardiomyopathy or heart failure
Lin K et al. [32], J Nucl Cardiol. 2022	Clinical	^{68}Ga-FAPI-04	Diffuse uptake of FAPI in the left ventricle and left atrium, while no uptake was seen in the right heart in a patient with hypertensive heart disease
Other cardiomyopathies			
Siebermair J et al. [33], Eur Heart J Case Rep. 2022	Clinical	^{68}Ga-FAPI-46	Potential role of FAPI-PET in the treatment guidance of immunomodulatory therapy in CS
Guo W et al. [34], Radiology. 2022	Clinical	^{68}Ga-FAPI-04	Diffuse FAPI uptake in the left ventricle myocardium and tongue. Tongue biopsy results showed positive Congo red staining consistent with amyloid involvement
Wang X et al. [35], JACC Cardiovasc Imaging. 2022	Clinical	^{68}Ga-FAPI-04	FAPI-PET/CT is feasible in detecting myocardial fibroblast activation in patients with AL CA in correlation with myocardial remodeling
Treutlein C et al. [36], Eur J Nucl Med Mol Imaging. 2023	Clinical	^{68}Ga-FAPI-04	FAPI uptake visualizes fibroblast activation in systemic sclerosis -related MF and may be a diagnostic option to monitor cardiac fibroblast activity in situ
Si J et al. [37], Front Cardiovasc Med. 2022	Clinical	^{18}F-FAPI	In vivo visualization of fibroblast activation after eosinophilic myocarditis
Finke D et al. [38], Front Cardiovasc Med. 2021	Clinical	^{68}Ga-FAPI	High myocardial FAPi uptake in patients with typical clinical and serum hallmarks of myocarditis related to immune-checkpoint inhibitors therapy
Zhang X et al. [39], Eur J Nucl Med Mol Imaging. 2023	Clinical	^{68}Ga-FAPI	FAPI PET imaging may be used to detect ICI-associated myocarditis-induced heart failure

^{68}Ga-FAPi ^{68}Gallium 68-labeled fibroblast activation protein (FAP) inhibitor, *CAD* coronary artery disease, *MI* myocardial infarction, *LVEF* left ventricular ejection fraction, *CMR* cardiac magnetic resonance, *STEMI* ST-elevation myocardial infarction, *LGE* late gadolinium enhancement, *AMI* acute myocardial infarction, *LV* left ventricular, *HF* heart failure, *RV* right ventricular, *PAH* pulmonary arterial hypertension, *ICIs* immune checkpoint inhibitors, *PET* positron emission tomography, *PET/CT* PET computed tomography, *AL CA* light-chain cardiac amyloidosis, *MF* myocardial fibrosis

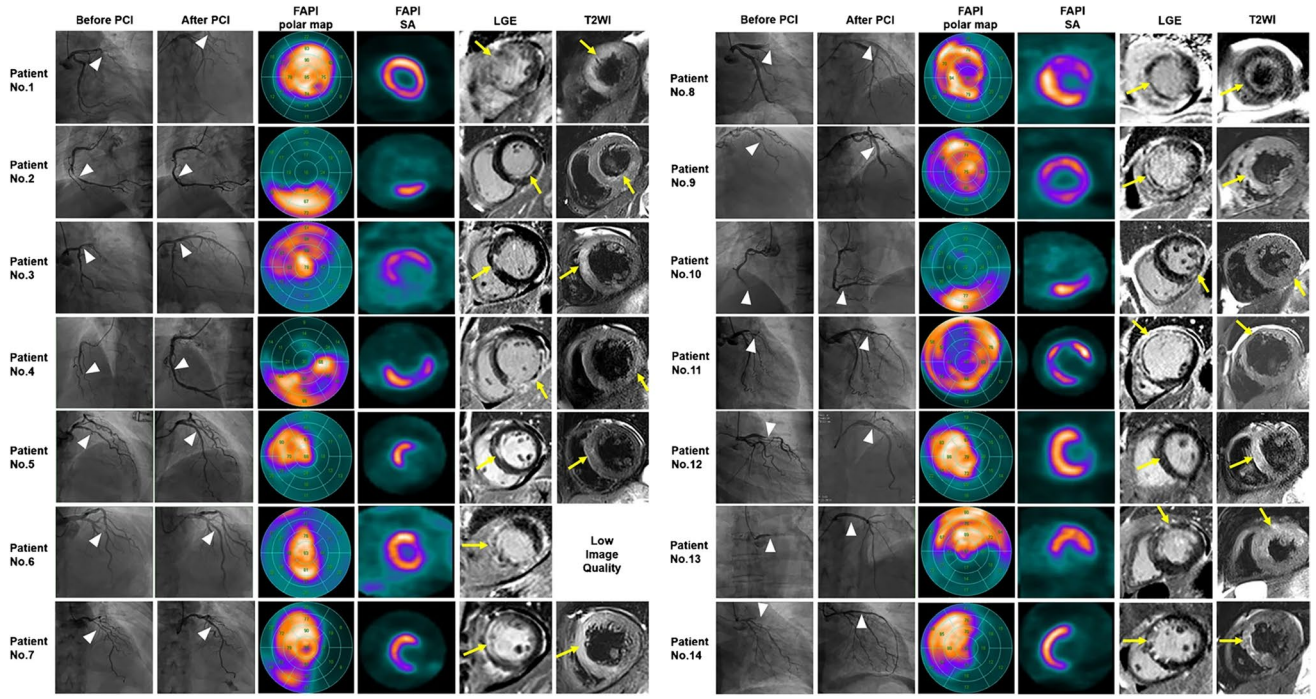

Fig. 1 Coronary angiographic images before (first column) and after PCI (second column) with the treated culprit vessel (white arrows). Polar maps (third column) and the selected short-axis images of FAPI (fourth column), LGE (fifth column), and T2WI (sixth column). FAPI uptake was observed in the culprit territory, which was larger than the corresponding edematous and infarcted area (yellow arrows). PCI percutaneous coronary intervention, FAPI fibroblast activation protein inhibitor, SA short-axis, LGE late gadolinium enhancement, T2WI T2-weighted imaging. Reprinted with permission of Springer from [17••]. No changes were made

related to the occurrence of adverse cardiac events. However, no correlation between either FAPi signal intensity or volume and the level of acute inflammation or myocardial damage-related markers was observed in the work by Zhang. This observation is consistent with other studies, wherein no correlation between FAPi uptake and the level of TGF-β1, TNF-α, IL-6, $_{hs}$CRP, CK_{peak}, and LDH_{peak} could be demonstrated [17••, 20•]. It is conceivable that the uptake of ^{68}Ga-FAPI within the myocardium reflects a different degree of ventricular remodelling, but, in order to fully understand its significance, further studies are needed to elucidate the interaction among other subtype of fibroblasts and macrophages.

Heart Failure in Non-ischemic Disease

Active fibroblasts and ventricular remodeling play an essential role in the onset and progression of heart failure (HF). In a rat model [23], activated fibroblasts in the heart and liver after pressure overload were linked in an early fibrotic environment, able to predict the occurrence of HF. Consistent results were reported in another translational study [24], wherein high FAPi uptake early after isoproterenol (ISO)-induced HF was reported, with a peak 7 days after HF induction. Over time, myocardial fibrosis invariably occurred and was associated to increased degree of myocardial injury. Of note, the degree of FAPi uptake decreased with the increase of myocardial fibrosis, thus suggesting that ^{68}Ga-FAPi PET selectively identifies active myocardial fibrosis. Hence, the detection of early FAP expression may assist treatment decision-making in HF patients.

Right Ventricular Imaging in Pulmonary Arterial Hypertension

The value of FAPi-PET was also investigated to directly visualize fibrotic remodeling of the right ventricle in patients with pulmonary arterial hypertension (PAH). Specifically, two case reports [25, 26] and two prospective studies [27, 28] showed significant tracer uptake of the right heart including the right ventricular free wall which correlated positively with wall thickness and negatively with right ventricular function. On the contrary, no ^{68}Ga-FAPi uptake of LV myocardium was seen in these studies. Additionally, a

significant positive correlation was observed between cardiac FAPi uptake and total pulmonary resistance and the level of N-terminal pro b-type natriuretic peptide [28].

Chemotherapy-Induced Cardiotoxicity

Some studies support the use of FAPi-PET in patients undergoing chemotherapy to assess cardiotoxicity [29•, 30]. In these reports, the described high ^{68}Ga-FAPi uptake within the LV myocardium in patients with previous systemic antineoplastic therapies may reveal FAP activation due to cardiotoxicity. Same considerations pertain to cardiac damage after radiotherapy. In another two studies, patients treated with anthracyclines or alkylating agents or patients with previous radiotherapy had high myocardial ^{68}Ga-FAPi uptake [13••]. Of note, it seems that FAPi-PET imaging can detect radiation-induced myocardial damage before evidence of decreased LVEF, with evident implications for early monitoring of cardiac toxicity [31].

Hypertrophic, Dilatated, and Hypertensive Cardiomyopathy

Due to the similar fibroblast-mediated pathophysiological mechanism leading to myocardial fibrosis, FAPi imaging was investigated in the assessment of myocardial injury in hypertrophic cardiomyopathy (HCM). In a prospective observational study, high myocardial FAPi uptake was predictive of increased risk of sudden cardiac death within 5 years [32]. Two case reports also highlighted the possible role of FAPi imaging in dilated cardiomyopathy [42] and hypertensive cardiomyopathy [33], showing increased uptake within the LV. However, the precise role of FAPi imaging in these conditions needs to be fully elucidated.

Other Cardiomyopathies

A recent study using ^{68}Ga-FAPi-46 PET/CT reported high sensitivity (87%) and specificity (90%) in the detection of fibroblasts activity in cardiac sarcoidosis (CS) [34]. Other case reports reported an intense FAP uptake in affected myocardial areas in patients with amyloidosis, related to ventricular remodeling [35, 36], which may provide complementary information on cardiac molecular characterization and staging of disease. Also, FAPi imaging was investigated in systemic sclerosis-related myocardial fibrosis [37], eosinophilic myocarditis (EM) [38] and in the assessment of myocarditis induced by checkpoint inhibitors (CI). In this latter setting, Finke et al. [39] report a high myocardial FAPi uptake in patients with typical clinical and serum hallmarks of myocarditis related to immune-checkpoint inhibitors therapy. Of note, ^{68}Ga-FAPi PET imaging may also be used to predict HF due to CI-related myocarditis, as recently described by Zhang et al. [43].

General Remarks

To now, evidences on the role of ^{68}Ga-FAPi PET/CT in cardiovascular imaging are scarce, but not poor. As a matter of fact, studies are mostly preliminary, but cumulating information indicates a clear potential in the diagnostic and prognostic assessment of patients with cardiovascular diseases.

To date, the most studied area of application of FAPi imaging is CAD, especially in the evaluation of post-AMI inflammatory alterations within the myocardium. The enhanced efforts in the latest years well fit the need for early markers of HF progression after AMI.

In this regard, increasing evidence suggests that inflammation plays a pivotal role in the progression to HF [44]. Among possible mechanisms of inflammation, the migration of macrophages after an insult plays conceivably a major role [22]. Early after an acute event, proinflammatory, M1-like macrophages are recruited, followed by the expression of reparative, M2-like macrophages [45]. While the former subtype is responsible for the production of pro-inflammatory molecules, including cytokines and proteases, the latter facilitates the secretion of factors stimulating angiogenesis and extracellular matrix reorganization, which are responsible for the promotion of fibrosis, as occurs in the post-infarction myocardial scar [46, 47].

Fibroblasts also possess a wide range of functions and phenotypes, which are likely to evolve over the healing process. But in contrast to the macrophage activation, which occurs immediately after the insult, the activation of myocardial fibroblasts is relatively delayed and sustained by TGF-β and other growth factors including platelet-derived growth factor [22, 48]. Consistent with this concept, there is evidence that distinct signatures of fibroblasts are expressed after AMI [49].

But if the expression of different fibroblasts follows a similar timecourse in the infarcted myocardium across individuals, but with conceivable, significant interindividual difference, how can we apply FAPi imaging in clinical practice? Is there a chance that we are not capturing the entire disease burden if we perform FAPi imaging at wrong time intervals after AMI? Furthermore, can we be absolutely sure that the interaction of different subtypes of fibroblasts does not play a more important role than FAP expression itself?

As a matter of fact, there is a contention on the correlation between FAPi uptake and the level of acute inflammation or myocardial damage-related markers. While some reports found no correlation [17••], another study demonstrated a correlation with markers of myocardial injury [20•]. This discrepancy represents a major issue for clinical applications, since the intensity of ^{68}Ga-FAPi uptake can have a therapeutic importance only if it highlights a subtending, intensive inflammation, which may be treated with immune-modulators.

An inconsistency in the peak time between these serum markers in the blood and that of myocardial ^{68}Ga-FAPI uptake can be an explanation but the influence of the interaction among other subtype of fibroblasts and/or macrophages requires further clarifications.

Besides its role in post-AMI setting, FAPi also brings the potential for the diagnostic and prognostic assessment of other cardiac diseases. However, the full role of FAPi imaging needs to be elucidated, as well as its performance in comparison to already established modalities such as fluorodeoxyglucose (FDG) PET and CMR.

Many trials have been registered in the latest months, and their results will clarify whether we now identified a workhorse in the prognostic assessment of patients with cardiac diseases or just a nice tool with academic interest but without any reasonable clinical application.

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Data Availability Data will be made available upon request.

Declarations

Human and Animal Rights and Informed Consent Not applicable for review papers.

Competing Interests The authors declare no competing interests.

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- • Of importance
- •• Of major importance

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