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Original Article

Machine learning-based CT fractional flow reserve assessment in acute chest pain: first experience

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Background: Computed tomography (CT)-derived fractional flow reserve (FFR_{CT}) enables the non-invasive functional assessment of coronary artery stenosis. We evaluated the feasibility and potential clinical role of FFR_{CT} in patients presenting to the emergency department with acute chest pain who underwent chest-pain CT (CPCT).

Methods: For this retrospective IRB-approved study, we included 56 patients (median age: 62 years, 14 females) with acute chest pain who underwent CPCT and who had at least a mild (≥25% diameter) coronary artery stenosis. CPCT was evaluated for the presence of acute plaque rupture and vulnerable plaque features. FFR_{CT} measurements were performed using a machine learning-based software. We assessed the agreement between the results from FFR_{CT} and patient outcome (including results from invasive catheter angiography and from any non-invasive cardiac imaging test, final clinical diagnosis and revascularization) for a follow-up of 3 months.

Results: FFR_{CT} was technically feasible in 38/56 patients (68%). Eleven of the 38 patients (29%) showed acute plaque rupture in CPCT; all of them underwent immediate coronary revascularization. Of the remaining 27 patients (71%), 16 patients showed vulnerable plaque features (59%), of whom 11 (69%) were diagnosed with acute coronary syndrome (ACS) and 10 (63%) underwent coronary revascularization. In patients with vulnerable plaque features in CPCT, FFRCT had an agreement with outcome in 12/16 patients (75%). In patients without vulnerable plaque features (n=11), one patient showed myocardial ischemia (9%). In these patients, FFR_{CT} and patient outcome showed an agreement in 10/11 patients (91%).

Conclusions: Our preliminary data show that FFR_{CT} is feasible in patients with acute chest pain who undergo CPCT provided that image quality is sufficient. FFR_{CT} has the potential to improve patient triage by reducing further downstream testing but appears of limited value in patients with CT signs of acute plaque rupture.

Keywords: Acute coronary syndrome (ACS); computed tomography angiography; fractional flow reserve; myocardial; machine learning

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Introduction

Acute coronary syndrome (ACS) refers to a spectrum of conditions compatible with acute myocardial ischemia and/or infarction usually reflecting an abrupt reduction in coronary blood flow (1,2). Patients may present with ST-segment elevation having myocardial infarction (STEMI) or without ST-segment elevation having either unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) (1,2). Prompt diagnosis of ACS in the emergency department (ED) is crucial as it is associated with high morbidity and mortality as well as frequent rehospitalization (3,4). Computed tomography (CT) dedicated for chest pain evaluation (hereafter called chest pain CT, CPCT) is considered beneficial in the evaluation of patients for whom diagnoses other than ACS are considered as well, such as pulmonary embolism or acute aortic syndrome (5-8). Compared to dedicated coronary CT angiography, CPCT provides anatomic coverage of the entire chest and contrast enhancement of both, the pulmonary and aortic/coronary circulation (5-8). Evaluation of coronary artery stenosis with CT can improve the triage of patients with acute chest pain in the ED and the efficiency of clinical decision making (9). In addition to coronary artery stenosis evaluation, CT has the potential to identify high-risk atherosclerotic plaque features that are associated with a higher likelihood of ACS, independent of clinical risk assessment and coronary artery stenosis assessment alone (10). Furthermore, CT enables the detection of acute plaque rupture eventually leading to coronary thrombosis and acute myocardial infarction (11). However, CT features of vulnerable plaques (being at risk for plaque rupture) and culprit lesions (being responsible for acute symptoms) may be similar and the degree of coronary artery stenosis may overlap (12-15).

Catheter-guided measurements of the fractional flow reserve (FFR) is the current gold standard to assess lesion-specific ischemia and to guide revascularization (16-18). Recently, FFR assessment based on coronary CT angiography (FFR_{CT}) has been introduced enabling the calculation of the FFR non-invasively (19-22). The clinical applicability of FFR_{CT} in patients with chronic coronary syndrome was the focus of several studies (20,22,23). Here, the potential role of FFR_{CT} for treatment guiding may further evolve with increasing use of coronary CT angiography as the first line imaging test in patients with suspected CAD (24). While most studies so far evaluated the accuracy and utility of FFR_{CT} in patients with chronic coronary syndrome, only few studies showed the feasibility of FFR_{CT} in patients with acute chest pain undergoing coronary CT angiography (10,25).

The aim of our study was to evaluate the feasibility and potential clinical role of FFR_{CT} in patients presenting to the ED with acute chest pain who underwent CPCT. We present the following article in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting checklist (available at http://dx.doi.org/10.21037/cdt-20-381).

Methods

Patient population

The research was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Local ethics committee approved this retrospective study (KEK-Nr.2015-00233). Written informed consent requirement was waived because of the retrospective nature of the research. Clinical decisions were not influenced by the results of this study. Between June 2012 and December 2018, 751 patients presenting with acute chest pain underwent dedicated CPCT at our institution. According to the clinical suspicion, CPCT was tailored to evaluate two or three of the following three disease entities: ACS, acute aortic syndrome, and pulmonary embolism. According to current recommendations, patients with indeterminate evaluation of ACS were referred to CPCT based on the clinical judgement of the emergency department physician and the cardiologist on-call taking into account all available information (1,2). Patients with ST-elevation in electrocardiography (ECG) or with clear elevation of cardiac biomarkers including high-sensitivity troponin were only referred to CPCT when the patient refused to undergo invasive coronary angiography (ICA) as an informed decision by the patient. Patients with arrhythmia were not excluded from the study.

Only patients who underwent CPCT including an evaluation of the coronary arteries (*Figure 1*) were retrospectively included (n=218, 29%). Patients with no relevant coronary artery stenosis <25% (n=141, 19%) and patients with a history of coronary revascularization (by either percutaneous coronary intervention or coronary artery bypass grafting) were excluded (n=21, 3%).

Each patient's electronic medical files was reviewed for cardiovascular risk factors, ECG changes, cardiac biomarkers, and any further cardiac imaging performed

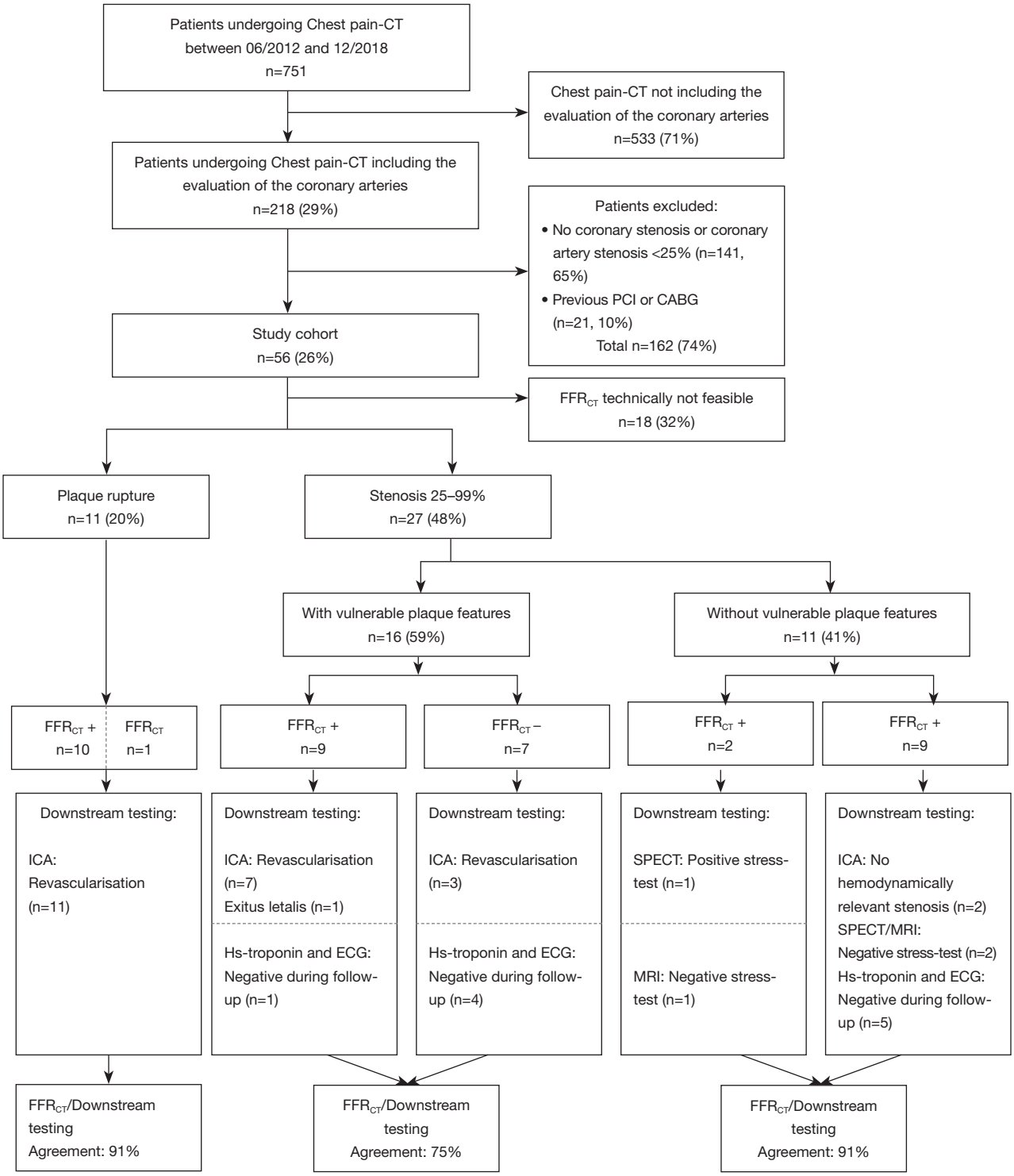

Figure 1 Study flow chart. A positive FFR_{CT} (FFR_{CT}+) result was defined as ≤0.8, a negative FFR_{CT} (FFR_{CT}–) as >0.8. CABG, coronary artery bypass grafting; CT, computed tomography; ECG, electrocardiogram; FFR_{CT}, CT-derived fractional flow reserve; ICA, invasive coronary angiography; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; SPECT, single-photon emission CT.

(including ICA; cardiac magnetic resonance imaging, MRI; and myocardial perfusion single-photon emission CT, SPECT) (26). The final diagnosis of ACS results from all information available within 3 months of follow-up. For our final cohort there was no missing data or loss to follow-up.

CT data acquisition

All scans were performed on a second-generation dual-source CT scanner (SOMATOM Flash, Siemens Healthineers, Forchheim, Germany). Sublingual nitroglycerin (isosorbiddinitrate, Isoket Spray, 25 mg/mL, UCB-Pharma, Brussels, Belgium) was administered prior to the scan. After performing a non-enhanced prospectively ECG-gated scan dedicated to calcium scoring, a contrast-enhanced, retrospectively ECG-gated CT scan with heart rate-dependent ECG-pulsing was performed as previously described (7). Contrast-enhanced CT images were reconstructed using sinogram-affirmed iterative reconstruction at strength level 3 with the following parameters: kernel, medium smooth convolution kernel (I30f); slice thickness, 0.75 mm; increment, 0.5 mm; field-of-view, 200×200 mm.

For subsequent image analysis, readers were blinded to clinical information and patient outcome.

CT evaluation

A board-certified radiologist with 7 years' experience in cardiovascular radiology (M Eberhard) assessed coronary arteries and the degree of stenosis according to the Coronary Artery Disease Reporting and Data System (CAD-RADS) (27). Correspondingly, coronary artery stenosis was subdivided into mild (25–49%), moderate (50–69%) and severe (70–99%). The same reader also searched for the presence of high-risk plaque features with the following definitions: Positive remodeling (remodeling index >1.1); low attenuation plaque (plaque attenuation <30 Hounsfield Units); spotty calcification (calcified plaque comprising <90° of the vessel circumference and <3 mm in length); napkin ring sign (central low attenuation plaque with peripheral higher CT attenuation) (27,28). Acute plaque rupture with coronary thrombosis was defined by the presence of hazy intraluminal hypodense material and positive remodeling of the involved coronary artery segment (29).

FFR_{CT}

For FFR_{CT} calculation we used an on-site machine learning-based algorithm (cFFR, version 3.2; Siemens Healthineers) (30). The machine learning algorithm was trained using a fully connected deep neural network architecture with four hidden layers on a large database of 12,000 synthetically generated coronary anatomies (19). The input layer had 28 neurons corresponding to the different features from the coronary tree and the hidden layers contained 256, 64, 16, and 4 neurons, respectively. The output layer had a single neuron with the linear activation function. Each layer was initially pretrained as an autoencoder. Subsequently, the model was validated in 87 patients against invasive FFR measurements and showed high accuracy (19). The preprocessing to generate an anatomical model of a patient's coronary tree is semiautomatic. The system automatically generates centerlines and afterwards luminal contours which can be interactively edited by the reader. In a third step the reader has to mark all coronary stenosis. Subsequently, features required for the machine learning-algorithm are automatically extracted from the reconstructed anatomical model. FFR_{CT} values are computed at all locations in the coronary tree and the resulting values are color coded in the anatomical model (19).

One reader (T Nadarevic) with 4 years' experience in cardiovascular radiology assessed FFR_{CT} on a dedicated workstation (Intel Xeon W-2125 CPU 4.00 GHz; 32.0 GB RAM). In a semi-automatic process (mean duration: 28±4 minutes), a coronary tree was created for each patient. A cut-off value of 0.80 was applied to distinguish between positive and negative lesion-specific ischemia (20,31).

Statistical analysis

Non-normally distributed and continuous data are presented as median and interquartile-range (IQR). Normally distributed data are presented as mean ± standard deviation. Categorical and ordinal variables are presented as numbers and percentages. Comparison of non-parametric continuous data was performed applying the Mann-Whitney-U-test or student's *t*-test where appropriate. For all analyses, a two-tailed P value <0.05 was considered statistically significant. All calculations were performed using commercially available software (SPSS version 25; IBM Corp., Armonk, NY, USA).

Results

A total of 56 patients (median age: 62 years, 14 females) were included in this study. *Table 1* shows detailed patient

Table 1 Patient demographics

Characteristic	Patient population (n=56)
Age (years)	62; 52–72
Body mass index (kg/m^2)	27.4±5.4
Female, n (%)	14 [25]
Diabetes, n (%)	9 [16]
Arterial hypertension, n (%)	43 [78]
Dyslipidemia, n (%)	26 [46]
Smoker, n (%)	29 [52]
Known CAD, n (%)	5 [9]
Previous myocardial infarction, n (%)	4 [7]
History of pulmonary embolism, n (%)	4 [7]
Heart rate during CT (bpm)	71; 61–85
Coronary Agatston Score	167; 27–402
Attenuation of the aortic root (HU)	350±76

Age and heart rate during CT and the coronary Agatston Score are given as median; inter-quartile-range. Body mass index and attenuation of the aortic root at the level of the coronary ostia are given as mean ± standard deviation. bpm, beats per minute; CAD, coronary artery disease.

characteristics. Five patients had a coronary Agatston Score of 0 (9%). One of these patients showed acute plaque rupture (n=1/5; 20%) and another showed vulnerable plaque features (n=1/5; 20%). Thereafter, both of these patients underwent ICA with coronary revascularization.

Feasibility of FFR_{CT}

FFR_{CT} was technically not feasible in 18 patients (32%). These patients showed a significantly higher heart rate (median 81 bpm, IQR: 71–95 bpm) compared to the remaining 38 patients (median 67 bpm, IQR: 60–78 bpm, P<0.05). There were no significant differences in the coronary Agatston score (median 167, IQR: 33–392 versus 156, IQR: 6–513; P=0.78) and attenuation of the aortic root (353±74 versus 343±82 HU; P=0.63) between patients with and without feasible FFR_{CT} analyses.

Plaque rupture and patient outcome

11 patients (29%) showed CT characteristics of acute plaque rupture (*Figure 2*). All of the 11 patients underwent immediate ICA with coronary revascularization. One of these 11 patients (9%) showed a negative FFR_{CT} >0.8 (see *Figure 1*, *Table 2*).

CPCT with FFR_{CT} measurements and clinical outcome

In the remaining 27 patients (71%), each 9 patients (33%) showed a mild, moderate or severe coronary artery stenosis (*Figure 3*). Sixteen of these 27 patients (59%) showed at least one vulnerable plaque feature, and 11 of these 27 patients (41%) had a positive FFR_{CT} ≤0.8. FFR_{CT} and the clinical diagnosis of ACS showed an agreement of 81% (n=21/27).

In patients showing vulnerable plaque features in CT (n=16), 10 patients underwent ICA with coronary revascularization (63%), one patient (6%) died within 3 days of CPCT (non-ST-elevation myocardial infarct and decompensated COPD), and five patients (31%) showed negative ECG and cardiac biomarkers during follow-up (see *Figure 1*). In these 16 patients, FFR_{CT} ≤0.8 correctly predicted ACS in 8 patients (n=8/9 patients, 89%) and FFR_{CT} >0.8 correctly ruled-out ACS in 4 patients (n=4/7 patients, 57%). This results in an agreement of FFR_{CT} and ACS in 75% of patients (n=12/16) with vulnerable plaque features in CPCT.

In patients without vulnerable plaque features (n=11), one patient showed myocardial ischemia (9%), two patients showed no relevant coronary artery stenosis in ICA (18%), three patients showed no myocardial ischemia evaluation (27%), and five patients showed negative ECG and cardiac biomarkers during follow-up (45%) (*Figure 1*). In these 11 patients, FFR_{CT} ≤0.8 (n=2) correctly predicted ACS/myocardial ischemia in one patient (50%) and FFR_{CT} >0.8 (n=9) correctly ruled-out ACS/myocardial ischemia in 9 patients (100%). This results in an agreement of FFR_{CT} and ACS/myocardial ischemia in 91% of patients (n=10/11) without vulnerable plaque features in CPCT. CT evaluation of plaque rupture, anatomical stenosis, and high-risk plaque features stratified according to FFR_{CT} results are shown in *Table 2*.

Discussion

Our preliminary experience with FFR_{CT} in patients with acute chest pain undergoing CPCT confirms and expands previous knowledge in the field: (I) non-invasive FFR_{CT} calculations are feasible in acute chest pain patients undergoing CPCT showing mild to severe coronary artery stenosis, provided that the image quality is sufficient; (II)

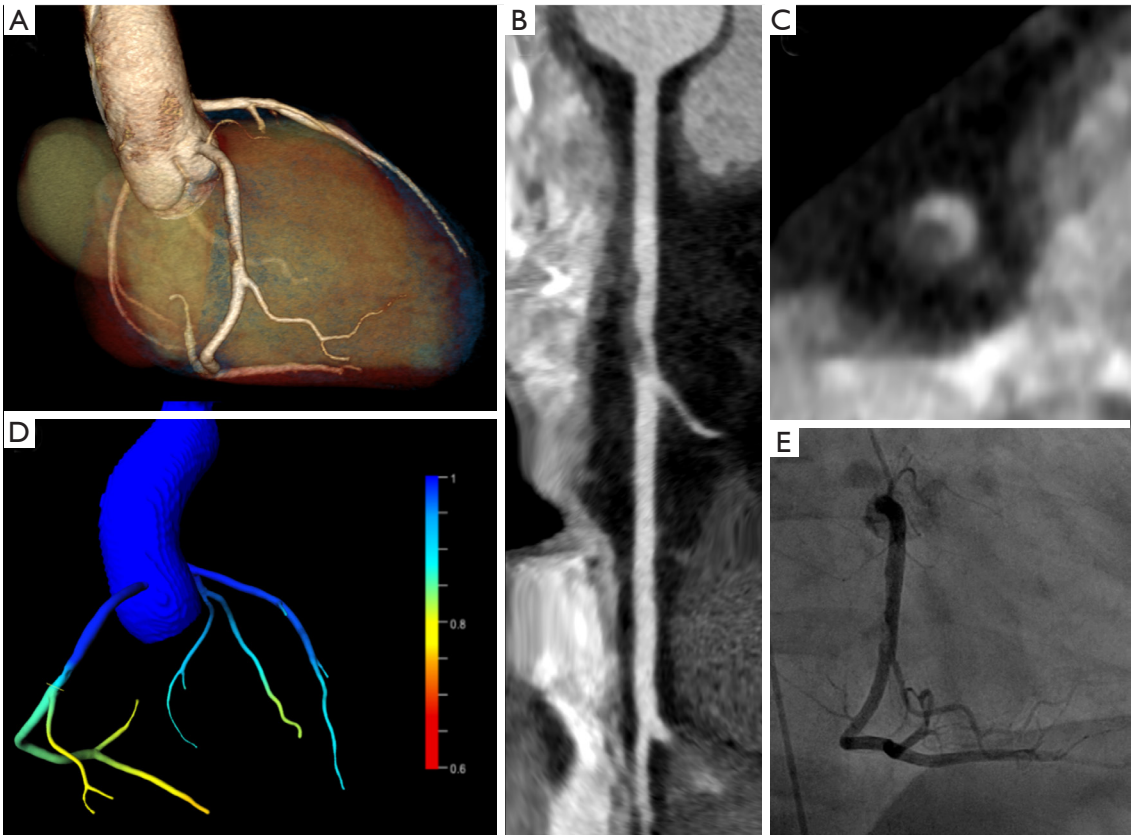

Figure 2 A 32-year-old male patient presenting to the emergency department with acute chest pain, slightly elevated cardiac biomarkers, and a history of pulmonary embolism. After leaving the emergency department against medical advice, the patient returned two days later with persistent symptoms. Cardiovascular risk factors were a positive family history, dyslipidemia, and smoking. The patient refused to undergo invasive coronary angiography (ICA) but agreed on having CT. Chest-pain CT was performed to rule-out recurrent pulmonary embolism and acute coronary syndrome. CT showed hazy intraluminal hypodense material in the mid RCA with positive remodelling, suspicious for acute plaque rupture (A-C). Lesion specific FFR_{CT} was 0.89 (D), which indicates the absence of lesion-specific ischemia. ICA confirmed a thrombus in the mid RCA most probably due to acute plaque rupture (E). Subsequent coronary intervention with stent placement was performed.

FFR_{CT} shows no added value in patients with CT signs of acute plaque rupture; (III) a FFR_{CT} <0.8 indicating lesion-specific ischemia was associated with vulnerable plaque features on CT and with ACS in patients lacking signs of acute plaque rupture, and (IV) FFR_{CT} has the potential to reduce further downstream testing in patients presenting to the ED with acute chest pain who show no signs of acute plaque rupture in CT.

Machine learning algorithms have shown promising results to improve diagnostic performance and specificity of coronary CT angiography (20,23,32-34). Advanced computational processing and fluid dynamics analysis derived from CT angiography datasets allow for the evaluation of the hemodynamic significance of a coronary artery stenosis showing a high agreement with FFR measurements from ICA (20,23). In patients with chronic coronary syndrome, a FFR_{CT} >0.8 indicates that a stenotic lesion is unlikely to be hemodynamically significant and without further downstream testing for ischemia, medical treatment of these patients appears safe (31). This strategy may not only work in patients with chronic but also in those with acute chest pain. However, the application of FFR_{CT} in patients with acute chest pain is not well understood so far.

The first, intriguing question in this context is whether image quality of CT in the acute setting is sufficient for FFR_{CT} image post-processing. Several multicenter trials

Table 2 CT evaluation

	FFR_{CT} >0.8	FFR_{CT} ≤0.8
Plaque rupture (n, %)	1 [9]	10 [91]
CT anatomical evaluation		
Mild stenosis (n, %)	9 [100]	0 [0]
Moderate stenosis (n, %)	6 [67]	3 [33]
Severe stenosis (n, %)	1 [17]	8 [83]
CT high-risk plaque features		
Positive remodeling (n, %)	7 [44]	9 [56]
Low attenuation plaque (n, %)	1 [33]	2 [67]
Spotty Calcification (n, %)	1 [50]	1 [50]
Napkin ring sign (n, %)	0 [0]	1 [100]

CT evaluation of plaque rupture, anatomical stenosis and high-risk plaque features stratified according to FFR_{CT} results. A positive FFR_{CT} result was defined as ≤0.8, a negative FFR_{CT} as >0.8. Coronary artery stenosis was subdivided into mild (25–49%), moderate (50–69%) and severe (70–99%).

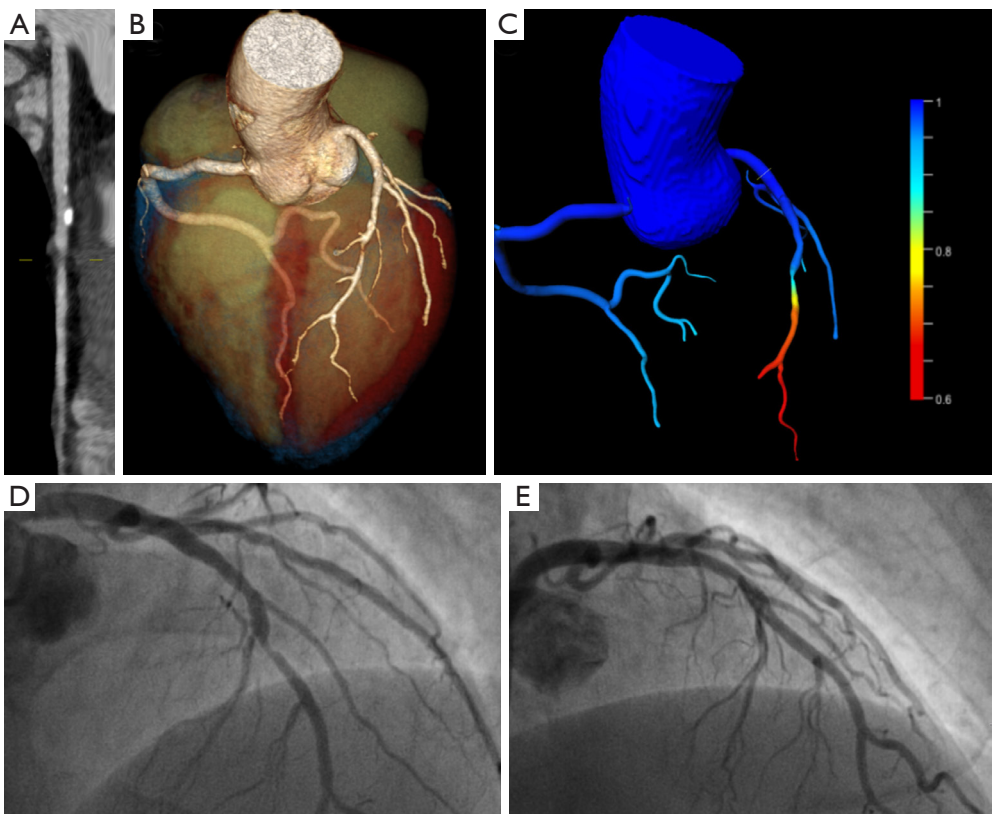

Figure 3 A 52-year-old male patient presenting to the emergency department with acute chest pain, dyspnea, and vagal symptoms after a transatlantic flight. The patient had a short episode of dyspnea and chest pain while running some hours before the flight. Laboratory tests revealed borderline troponin elevation with normal creatine kinase levels. ECG showed sinus rhythm with ST-segment depression in leads I and II. To rule out pulmonary embolism, acute aortic syndrome, and acute coronary syndrome the patient underwent chest-pain CT. CT ruled out acute aortic syndrome and pulmonary embolism, but showed a severe stenosis in the mid LAD (A and B) with a lesion-specific FFR_{CT} of 0.73 (C). Invasive coronary angiography confirmed an 80% stenosis of the mid LAD (D), which was successfully treated with a bioabsorbable vascular scaffold (E).

reported that 67–89% of coronary CT angiography datasets in patients evaluated for chronic coronary syndrome were of sufficient image quality for FFR_{CT} calculation (21,23). In patients with acute chest pain being part of the ROMICAT II-trial, FFR_{CT} computation was feasible in 59% of patients (10), which suggests a comparably reduced image quality of CT angiography in patients in the acute setting as opposed to the often elective, out-patients with chronic coronary artery syndrome. In our study, FFR_{CT} was feasible in 68% of patients undergoing CPCT, being slightly higher than the 59% reported by Ferencik *et al.* (10). These overall lower rates of technically feasible FFR_{CT} in patients with acute chest pain may be partly explained by higher heart rates in the emergency setting (median 71 bpm in our study). Accordingly, patients where FFR_{CT} was not feasible showed a significantly higher heart rate (median 81 bpm) compared to those in which FFR_{CT} was feasible (median 67 bpm). In the emergency setting, acute pain, dyspnea, and anxiety may further contribute to reduced image quality in CPCT. Of note, in our patient cohort there was no administration of oral and/or intra-venous beta-blockers prior to CPCT. Chinnaiyan *et al.* reported a high rate of FFR_{CT} feasibility (97%) in patients undergoing premedication with oral and/or intra-venous beta-blockers and a target heart rate <60 bpm for coronary CT angiography (25). This is in line with Pontone *et al.* who reported that a low heart rate is a prerequisite for successful FFR_{CT} analysis (21).

The second issue arising with application of FFR_{CT} in patients with acute chest pain is time efficiency. In an acute setting, FFR_{CT} calculation algorithms must be available on-site due to time constraints. Typically, these calculations take around 30–40 minutes (30). In our study, FFR_{CT} calculations took on average 28 minutes per patient. Chinnaiyan *et al.* applied a different, commercially available approach for FFR_{CT} which had the drawback that median turnaround times were above 2.5 hours (25). The average time needed to accomplish the on-site machine learning algorithm used in our study was recently reported as 2.4 seconds on a workstation with a 3.4-GHz Intel i7 8-core processor (19). However, the need for repeated user interaction in the semi-automatic workflow to create a precise anatomical model of each patient's coronary tree was still time consuming (mean duration of 28 minutes in our study), which limits the routine clinical use of this new technique (19).

The perhaps most relevant clinical issue is the identification of patients who benefit most from FFR_{CT} calculations. Our preliminary results suggest that FFR_{CT} calculations are not meaningful in patients with acute plaque rupture and coronary thrombosis. As patients with acute plaque rupture need immediate coronary revascularization (2), we believe there is no clinical role for FFR_{CT} in these patients. This is shown in our study where all 11 patients with acute plaque rupture signs in CPCT were immediately revascularized. In contrast, one of these 11 patients had a negative FFR_{CT} >0.8 which could have been misleading since coronary vessels with acute plaque rupture are often not stenosed to a larger extent (11).

In our study, three patients having an FFR_{CT} >0.8 were finally diagnosed with ACS and underwent ICA with revascularization. Such false negative findings were described by Ferencik *et al.* as well (10). Importantly, all these three patients showed vulnerable plaque features on CT. Puchner *et al.* (35) reported that the presence of vulnerable plaque features on CT increases the likelihood of ACS independent from stenosis severity and clinical risk assessment. This indicates that vulnerable plaque features should be taken into account when evaluating patients with acute chest pain in CT, beyond an assessment of stenosis grade and FFR_{CT} alone (14). In our patient cohort, FFR_{CT} was not used for clinical decision making. However, we found a strong correlation of FFR_{CT} with patient outcome including the results from ICA, revascularization, non-invasive cardiac imaging tests, and final clinical diagnosis. Especially in the subgroup of patients showing no vulnerable plaque features in CT, we found a high agreement rate of 91%, which indicates that FFR_{CT} may help avoiding further downstream testing in patients with acute chest pain. Our data show that FFR_{CT} is feasible not only on dedicated coronary CT angiography examinations (10,25) but also on CPCT performed to rule-out ACS, acute aortic syndrome, and pulmonary embolism.

Limitations

Our study has some limitations. First, the retrospective study design has inherent shortcomings and our results may reflect local practice being not generalizable to other institutions. Moreover, differences in patient demographics in other hospitals may lead to different results. Second, the number of finally included patients was rather low and our results need to be confirmed in larger, prospective outcome studies. In these studies the value of FFR_{CT} analysis should be assessed in comparison to clinical risk scores such as the TIMI (Thrombolysis in Myocardial Infarction) score.

Third, ICA (including invasive FFR measurements) or functional myocardial stress testing were not systematically performed in all patients. Fourth, we assessed the culprit lesions in a dichotomous way but did not analyze the presence, absence or degree of each individual vulnerable plaque features in more detail. Also, we did not assess quantitative measures of vulnerable plaque features since our patient cohort was too small for this purpose. Fifth, results were analyzed on a per-patient but not on a per-vessel level. Finally, the final study cohort showed a gender imbalance with only 25% women.

Conclusions

Our study indicates that non-invasive FFR_{CT} calculations are feasible in acute chest pain patients undergoing CPCT, provided that image quality is sufficient. In combination with the assessment of vulnerable plaque features FFR_{CT} has the potential to improve the triage of patients presenting to the ED with acute chest pain by reducing downstream cardiac imaging testing. In contrast, FFR_{CT} appears to have no added value in patients with CT signs of acute plaque rupture. Certainly, our preliminary results need to be confirmed in larger, prospective clinical outcome studies.

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Footnote:

Reporting Checklist: The authors present the study in accordance with the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/cdt-20-381

Data Sharing Statement: Available at http://dx.doi.org/10.21037/cdt-20-381

Peer Review File: Available at http://dx.doi.org/10.21037/cdt-20-381

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cdt-20-381). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The research was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Local ethics committee approved this retrospective study (Kantonale Ethikkommission Zürich, KEK-Nr.2015-00233). Written informed consent requirement was waived because of the retrospective nature of the research.

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