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Downstream resource utilization following hybrid cardiac imaging with an integrated cadmium-zinc-telluride/64-slice CT device

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Abstract: **PURPOSE:** Low yield of invasive coronary angiography and unnecessary coronary interventions have been identified as key cost drivers in cardiology for evaluation of coronary artery disease (CAD). This has fuelled the search for noninvasive techniques providing comprehensive functional and anatomical information on coronary lesions. We have evaluated the impact of implementation of a novel hybrid cadmium-zinc-telluride (CZT)/64-slice CT camera into the daily clinical routine on downstream resource utilization. **METHODS:** Sixty-two patients with known or suspected CAD were referred for same-day single-session hybrid evaluation with CZT myocardial perfusion imaging (MPI) and coronary CT angiography (CCTA). Hybrid MPI/CCTA images from the integrated CZT/CT camera served for decision-making towards conservative versus invasive management. Based on the hybrid images patients were classified into those with and those without matched findings. Matched findings were defined as the combination of MPI defect with a stenosis by CCTA in the coronary artery subtending the respective territory. All patients with normal MPI and CCTA as well as those with isolated MPI or CCTA finding or combined but unmatched findings were categorized as "no match". **RESULTS:** All 23 patients with a matched finding underwent invasive coronary angiography and 21 (91%) were revascularized. Of the 39 patients with no match, 5 (13%, $p < 0.001$ vs matched) underwent catheterization and 3 (8%, $p < 0.001$ vs matched) were revascularized. **CONCLUSION:** Cardiac hybrid imaging in CAD evaluation has a profound impact on patient management and may contribute to optimal downstream resource utilization.

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**Downstream resource utilization following hybrid cardiac imaging with an integrated
Cadmium-Zinc-Telluride/64-slice CT device**

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Key words: Downstream resource utilization, CZT, SPECT, cardiac hybrid imaging

Abstract

Purpose Low yield of invasive coronary angiography and unnecessary coronary interventions have been identified as key cost drivers in cardiology for evaluation of coronary artery disease (CAD). This has fuelled the search for non-invasive techniques providing comprehensive functional and anatomic information on coronary lesions. We have evaluated the impact of implementation of a novel hybrid Cadmium-Zinc-Telluride (CZT)/64-slice CT camera into daily clinical routine on downstream resource utilization.

Methods Sixty-two patients with known or suspected CAD were referred for same-day single-session hybrid evaluation with CZT myocardial perfusion imaging (MPI) and coronary CT angiography (CCTA). Hybrid MPI/CCTA images from the integrated CZT/CT camera served for decision making towards conservative versus invasive management. Based on the hybrid images patients were classified into those with and those without matched findings. Matched findings were defined as the combination of MPI defect with a stenosis by CCTA in the coronary artery subtending the respective territory. All patients with normal MPI and CCTA, as well as those with isolated MPI or CCTA finding or combined but unmatched findings were categorized as “no match”.

Results All 23 patients with a “matched” finding underwent invasive coronary angiography and 21 (91%) were revascularized. Of the 39 patients with “no match” 5 (13%, $p < 0.001$ vs. “matched”) underwent catheterization and 3 (8%, $p < 0.001$ vs. “matched”) were revascularized.

Conclusions Cardiac hybrid imaging in CAD evaluation has a profound impact on patient management and may contribute to optimal downstream resource utilization.

Introduction

In clinical practice diagnosis of coronary artery disease (CAD) has been based on the presence of a luminal narrowing of greater than 50 % documented by invasive coronary angiography catheterization (CATH). However, it has been recognized over the last decade that many factors other than lumen size and its narrowing which cannot be comprehensively elucidated by coronary angiography alone may determine whether or not an anatomic coronary lesion induces ischemia. Therefore, decision-making towards revascularization without proof of ischemia has been recently challenged. In fact, modern guidelines for coronary revascularization [1] stipulate that comprehensive evaluation including proof of ischemia is mandatory for prognostically relevant target vessel revascularization in chronic stable CAD.

Nuclear myocardial perfusion imaging (MPI) is a well-established method for the evaluation of myocardial ischemia and coronary computerized tomography angiography (CCTA) has been established over the past years as a clinical tool for the assessment of coronary anatomy. The combination of MPI with CCTA has been found to be a valuable gate-keeper for invasive coronary angiography [2] and may help to increase the low yield of elective invasive diagnostic coronary angiography (currently less than 40%) [3]. Cardiac hybrid imaging has emerged as one of the latest methodological advancements, integrating information on anatomy (CCTA) with that from MPI into hybrid images [4]. This allows to directly relating individual myocardial perfusion territories to the subtending coronary arteries. Most studies on hybrid MPI/CT imaging are based on fusion of data from a separate gamma camera and a standalone CT-scanner, as the unfavourable discrepancy of scan length (short CT and long MPI acquisition time) was hampering the widespread use of hybrid SPECT/CT devices in daily clinical routine. With the introduction of new gamma cameras using Cadmium-Zinc-Telluride (CZT) detector technique [5-8], scan time has been reduced substantially down to few minutes [9, 10]. This has paved the way for hybrid SPECT/CT scanners integrating a CZT gamma camera with a high end 64-slice CT device and has increased the interest in cardiac fusion imaging, further supported by recent results confirming the diagnostic strength [4, 11] and the prognostic value [12] of cardiac hybrid imaging. However, data on the added clinical value of hybrid

cardiac CZT/CT imaging in the decision making for the appropriate treatment strategy is lacking. The aim of the present study was to evaluate in daily clinical routine the impact of hybrid cardiac MPI and CCTA imaging obtained with an integrated ultrafast CZT/CT device on downstream resource utilisation such as invasive coronary angiography and revascularization.

Material and Methods

Patients and Study Protocol

We included 62 patients without history of prior coronary artery bypass graft (CABG) who were consecutively referred for the assessment of known or suspected CAD for a same-day single-session hybrid scan with CZT myocardial perfusion imaging (MPI) and CCTA to obtain hybrid cardiac images. All patients were scanned on a CZT/64-slice CT hybrid camera (Discovery NM/CT 570c, GE Healthcare) and the integrated CZT/CT images were reported to the referring physicians who made a decision towards invasive CATH versus conservative management based on the hybrid imaging finding on the one side and including the clinical history and the symptoms on the other hand. Similarly, in the catheterization laboratory the interventional cardiologist based his/her decision towards revascularization on the hybrid images and the clinical history, integrating the angiographic findings including fractional flow reserve at the operators' discretion into the clinical decision-making. Downstream resource utilization within 60 days triggered by the hybrid imaging was assessed including: decision for conservative treatment, invasive angiography, and revascularization procedure (CABG or percutaneous coronary intervention, PCI). From each study participant written informed consent was obtained for the use of their imaging and clinical data for research purposes as approved by the institutional review board.

Image Acquisition

All patients underwent one-day pharmacological stress/rest SPECT-MPI protocol according to the guidelines of the European Association of Nuclear Medicine [13] with adenosine (0.14 mg/kg/min over 6 min) while in patients with contraindications to adenosine (n=16) we used dobutamine (incrementally administered, starting at 5 µg/kg per minute and increasing at 1 minute intervals to a maximal dose of 60 µg/kg per minute until 85% of the age-predicted heart rate had been achieved) according to daily clinical routine in our lab. Approximately 60 minutes after injection of ^{99m}Tc-tetrofosmin (332±36 MBq), stress MPI images were acquired (5 minutes) using the CZT/CT camera. This was followed by acquisition of rest MPI with the identical acquisition protocol several minutes

[14] after administration of a three times higher dose of ^{99m}Tc -tetrofosmin (955 ± 169 MBq). MPI scans were acquired using a multipinhole collimator (effective diameter aperture of 5.1 mm) and 19 stationary detectors simultaneously imaging 19 different views of the heart as previously reported. In brief, each detector contains 32×32 pixelated (2.46×2.46 mm) CZT elements; the system design allows acquisition without detector or collimator motion, and a 10% symmetrical energy window at 140 keV was used [9]. A low-dose CT scan was performed for attenuation correction of SPECT-MPI, which also allows calculation of calcium scoring [15]. Thereafter, all patients underwent contrast-enhanced CCTA with prospective ECG-triggering as previously reported [16-18]. Intravenous metoprolol (2.5 to 25 mg) was administered prior to the examination if necessary in order to obtain optimal image quality for CCTA (target heart rate <65 bpm). All patients received 2.5 mg isosorbiddinitrate sublingually 2 min prior to the CCTA scan. MPI and CCTA images were fused on a dedicated workstation (Advantage Workstation 4.3, GE Healthcare) projecting the MPI images on the left ventricular epicardial surface obtained from the CCTA using the CardIQ Fusion software package (GE Healthcare) as previously validated [19, 20]. The 3D volume rendered fusion images enable a panoramic view of the coronary artery tree projected onto the left ventricular myocardial perfusion territories. Cardiac hybrid images can be displayed in standard anterior, posterior, lateral and apical view and in freely selectable angles for standardized documentation and reporting. Effective radiation dose for CCTA was calculated from dose-length product (DLP) using a conversion coefficient for the chest $k=0.014$ mSv/(mGy x cm); for SPECT-MPI a conversion factor of 0.0079 mSv/MBq was used.

Cardiac Hybrid Image Interpretation

Fused MPI and CCTA images were analysed by two experienced nuclear cardiologists by consensus with regard to functionally relevant coronary stenoses. For each patient, myocardial tomograms were grouped into 20 segments. The following 5-point scoring system was used to grade the segmental radionuclide uptake: 0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, 4 = absence of detectable tracer in a segment. A pathologic scan was defined as one with stress score ≥ 2 in two or more segments. If a stress defect was associated with a stress defect score of 4 with a rest score of 2 or a rest score ≤ 1 , a scan was classified as reversible perfusion defect. As patient

management should be ischemia-driven according to best clinical practice only reversible defects were considered for the following assignment into “matched” vs. “no matched” finding. A matched SPECT/CT hybrid cardiac imaging finding was defined as a reversible SPECT-MPI defect in a territory served by a coronary artery with a stenosis (defined as narrowing of the coronary luminal diameter $\geq 50\%$, Fig. 1). All patients with normal SPECT and CCTA, as well as those with isolated CCTA or MPI finding or combined but anatomically unmatched finding were categorized as “no match”.

Invasive Coronary Angiography Data Acquisition and Analysis

Invasive CATH was performed according to clinical standards by experienced interventional cardiologists. Segmentation of the coronary artery tree was performed as described for CCTA. A coronary stenosis was defined as a luminal narrowing $\geq 50\%$. This was based on visual assessment reflecting clinical routine in our and most other catheterization laboratories worldwide [21, 22]. The fractional flow reserve (FFR) was determined as the ratio of the simultaneously assessed pressure in the aorta and in the coronary artery distal of a stenosis during maximal hyperaemia (induced by intravenous adenosine administration via a central vein at $140 \mu\text{g/kg/min}$) [22].

Statistical Analysis

Quantitative variables were expressed as mean $\pm$ standard deviation and categorical variables as frequencies or percentages. SPSS 19.0 (SPSS, Chicago, IL) was used for statistical analysis. Chi-square test was applied to compare the revascularization rates between the two different patient groups. *P* values from chi square test of less than 0.05 were considered statistically significant.

Results

All patients (n=62) successfully underwent stress/rest CZT-MPI and CCTA using the CZT/CT camera. The patient characteristics are given in Table 1.

Overall, the CATH rate was 43% in the study population yielding 96%. CZT revealed 32 patients (52%) with an abnormal MPI with reversibility in 26 patients, while CCTA documented a coronary stenosis in 42 patients (68%) excluding CAD in 20 patients (32%). Three cases with (false) positive SPECT were corrected into negative by normal CCTA findings. Conversely, a coronary stenosis $\geq 50\%$ in CCTA but without stress-induced regional perfusion defect was found in 17 patients while 19 patients had a normal finding in both CCTA and MPI. Cardiac hybrid imaging revealed a matched perfusion defect in 23 patients (38%) whereas 39 patients (63%) had no matched findings. The measurement of FFR was performed in 9 patients (in 12 coronary lesions).

During follow-up, all patients with matched cardiac hybrid findings (n=23) were referred to CATH of whom 21 (91%, Fig. 2) subsequently underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Of the two patients without revascularization one had normal coronary arteries by CATH and the second patient had a small MPI defect and invasive assessment revealed a stenosis with normal fractional flow reserve ($\text{FFR} \geq 0.8$) over two lesions, i.e. in the left anterior descending artery (0.82) and in the left circumflex artery (0.89) both of which did therefore not qualify for coronary revascularization [23]. Only 5 of the 39 patients (13%) with no matched hybrid finding (Fig. 2) were sent to CATH and 3 (8%) were revascularized. The reasons for referring patient to CATH without matched hybrid finding were either severe CAD (left main or three vessel disease) $\geq 80\%$ (n=2) or massively elevated Agatston coronary calcium scoring (> 1000 ; n=3). The latter has recently been shown to unmask obstructive CAD in patients with normal SPECT-MPI [24]. Revascularization was subsequently performed in three patients despite lack of matched finding as one patient revealed abnormal FFR over a lesion in the left anterior descending artery (0.69) and the other patients showed either severe coronary three vessel disease or severe stenosis of the left main artery. There was a significantly lower downstream CATH resource utilization in patients with no matched findings versus those patients with matched cardiac hybrid findings ($p < 0.001$). Due to subclinical CAD

(< 50% luminal narrowing) preventive medical intervention was installed in one patient, while in one patient such medication was withdrawn after excluding any lesion by CCTA.

The effective radiation dose for stress/rest SPECT-MPI was 10.2 ± 1.5 mSv, for attenuation correction 0.9 ± 0.1 mSv and for prospective triggered CCTA 1.8 ± 0.6 mSv.

Discussion

Our results demonstrate that cardiac hybrid imaging with a CZT/CT device allows efficient comprehensive evaluation of CAD. This has a profound impact on patient management and may contribute to optimal downstream resource utilization. In the present study we have shown that in 91% of patients with a matched finding in cardiac hybrid imaging coronary revascularization was performed whereas only 8% of patients without matched cardiac hybrid finding were revascularized.

With regard to resource utilization the use of hybrid imaging had a strong impact as 100% of patients with a match but only 13% of patients without match were referred to CATH. As a result, in the patient group with a match the CAD per CATH yield was 96% comparing favourably to the yield of less than 38% recently reported for a similar elective large population [3]. The high CAD yield in our study paved the way for the above mentioned high rate of revascularization per CATH (91%), which is far superior to figures reported in registries of most European countries, such as for example Germany (36%) [25].

An appropriate selection of patients who will benefit from invasive CATH and eventually from revascularization is crucial not only because of the costs of CATH but also because of its non-negligible rate of procedural in hospital morbidity and mortality [26, 27]. Although it has been for long time suggested [28] and repeatedly documented [22] that for best clinical practice functional assessment of coronary lesion is mandatory, invasive CATH has remained not only the gold standard for CAD detection but also for decision-making for or against need of revascularization. Our results show that hybrid cardiac imaging is an excellent gate keeper for further evaluation with CATH. In fact, the high yield of CAD and revascularization rate per CATH documents an appropriateness of invasive resource utilization far beyond that reported from large clinical routine registries [3, 25]. By contrast, resource utilization was very low in patients with no hybrid match, in whom decision towards invasive CATH (n=5) was mainly driven by extensive coronary calcification (> 1000 Agatston units), which has recently been shown to unmask CAD in patients without SPECT-MPI abnormalities. Therefore, in the present study a calcium score > 1000 triggered a CATH overruling the lack of a matched finding. In 3 of these 5 patients justification to revascularize was supported either by FFR or

the presence of severe multi-vessel disease including main stem involvement [2]. The clinical value of comprehensive CAD assessment by hybrid CZT/CT imaging lies in the improvement of evidence-based patient selection for coronary revascularization [12, 29]. Although coronary interventions have shown to successfully reduce ischemic symptoms and, therefore, improve patients' quality of life, periprocedural adverse events remain important considerations, particularly in low risk populations. In stable CAD populations revascularizations have failed to confer a prognostic superiority compared to optimal medical therapy [30-33]. However, in patients with moderate to large ischemia revascularization may be the most effective strategy to reduce the amount of jeopardized myocardium and, consequently, improve prognosis [34]. As hybrid findings have shown to be superior in predicting adverse events over isolated findings [12] it appears appropriate that these findings are the predominant target of revascularization. In this context our results show that the implementation of hybrid CZT/CT camera in daily clinical routine confers an added value for evidence-based decision making and optimization of adequate downstream resource utilization. Patients with intermediate to high pre-test probability are among those who most likely may benefit from non-invasive evaluation by hybrid imaging. However, in view of the fact that most patients referred to elective invasive coronary angiography reveal normal coronary arteries, even lower pre-test probability patients may be candidates for a hybrid approach as long as unnecessary invasive angiographies can be avoided. A larger study would be needed to provide final proof of cost-effectiveness of the hybrid method, which was beyond the scope of the present pilot study.

We acknowledge the following limitations: A potential limitation of the present study is the fact that all patients underwent two non-invasive tests cumulating radiation exposure to the patients. However, several algorithms may be implemented into hybrid imaging such as for example stress only MPI [35] to reduce radiation. In addition, CZT cameras offer the potential of a low-dose/low-dose one-day protocol as the count-rate linearity allows subtraction of the counts of the first scan avoiding the need for a 3-fold increase of the second scan [36]. Finally, although patients were included consecutively, there was no randomization to different treatment options due to the observational nature of this pilot study on the downstream resource utilization. However, our results support the notion that use of a CZT/CT hybrid device in daily clinical routine may favourably affect resource utilization.

Nevertheless this may also depend on the awareness of the clinicians about the availability and performance of hybrid imaging as well as on the clinical environment accepting non-invasive imaging as guidance for revascularization.

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Conflict of interest

None declared.

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Table and Figure Captions

Table 1 Patient characteristics.

Patient baseline characteristics (<i>n</i> = 62)	
Characteristic	Value
Male, <i>n</i> (%)	47 (76)
Age (years)	
Mean±SD	62±10
Range	40-86
BMI (kg/m ²)	
Mean±SD	28±5
Range	19-46
Cardiovascular risk factors, <i>n</i> (%)	
Obesity (BMI > 30 kg/m ²)	18 (29)
Diabetes mellitus	10 (16)
Smoking	18 (29)
Hypertension	42 (68)
Dyslipidemia	35 (56)
Positive family history	22 (35)
Clinical symptoms, <i>n</i> (%)	
Typical angina pectoris	20 (32)
Atypical chest pain	3 (5)
Dyspnoea	8 (13)
No cardiac symptoms	31 (50)
Clinical findings, <i>n</i> (%)	
Abnormal rest ECG	27 (44)
Abnormal stress ECG	29 (47)
Abnormal echocardiography	4 (6)
Previous cardiac events, <i>n</i> (%)	
Myocardial infarction	5 (8)
Percutaneous coronary intervention	22 (35)
Stent implantation	21 (34)
Current cardiac medication, <i>n</i> (%)	
Aspirin	46 (74)
Beta-blocker	27 (44)
ACE/angiotensin II inhibitor	28 (45)
Statin	41 (66)

Fig. 1 Cardiac hybrid image and angiographic finding. Coronary artery stenosis (white arrow head) in proximal left anterior descending artery is shown in CCTA (A, multiplanar and B, curved multiplanar reconstruction), cardiac hybrid imaging with normal perfusion at rest (E) and perfusion defect at stress (C) matching the territory of the coronary artery with stenosis (white arrow head), and invasive coronary angiography (D) confirming the coronary stenosis (white arrow head).

Fig. 2 Downstream resource utilization after cardiac hybrid imaging. CATH: invasive coronary angiography.