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The Potential Value of Hybrid Positron Emission Tomography/ Dual-Source Computed Tomography Imaging in Coronary Bypass Surgery

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ABSTRACT

Background: We evaluated how comprehensive assessment of coronary artery lesions and their hemodynamic relevance by means of hybrid positron emission tomography (PET) and computed tomography (CT) imaging would affect decision-making in coronary artery bypass surgery (CABG), compared with using invasive coronary angiography (ICA) alone.

Methods: After undergoing ICA, 27 patients (21 men and 6 women; mean SD age, 66 ± 10 years) planned for cardiac surgery were scheduled for myocardial perfusion stress/rest evaluation with [13N]ammonia PET and CT coronary angiography. Only ICA was available to the surgeon. Postoperatively, the performed CABG was compared with the hypothetical strategy based on hybrid PET/CT findings (regional coronary flow reserve [CFR], myocardial perfusion defects). Procedures included CABG (n = 18) alone, CABG combined with valve replacement (n = 6), and CABG combined with isolated valve replacement (n = 3). A total of 56 bypass grafts (28 venous and 28 arterial) and 66 distal anastomoses were placed.

Results: CT evaluation showed 93% concordance (66/71) with ICA regarding significant stenoses, with sensitivity, specificity, positive predictive value, and negative predictive value of 93.1%, 98.7%, 94.4%, and 98.4%, respectively. In the PET scan, 16 patients had 1 ischemic region, and 12 patients had 1 scar region, including 5 patients who presented with mixed conditions (scar and ischemia). One patient had a completely normal myocardium. Compared with the performed surgery, PET/CT fusion evaluation showed that of the performed anastomoses, 48% had documented ischemia (with a CFR <2 in 86%), 38% were nonischemic (although a CFR value <2 was found in 78%), and 14% had scar tissue (fixed perfusion defect).

Conclusions: Although <50% of bypasses were placed to areas with myocardial ischemia, the CFR was low in the majority of nonischemic regions, a finding that may have important prognostic relevance. PET/CT fusion imaging could potentially influence planning for CABG and provide incremental prognostic information.

INTRODUCTION

Invasive coronary angiography (ICA) is commonly considered the gold standard for the diagnosis of coronary artery disease (CAD) [Hecht 2009]. In addition to the detection of coronary stenoses and the assessment of regional and global myocardial wall motion, ICA also allows percutaneous coronary intervention (PCI) in the same session. However, ICA provides only purely luminal anatomic information; it does not offer insights into coronary plaque quality or information on the physiological relevance of a stenotic coronary lesion. Therefore, the clinical guidelines recommend noninvasive ischemia testing prior to any kind of elective revascularization [Gibbons 2003; Fox 2006].

Computed tomography (CT) can be used for the noninvasive detection of CAD with high accuracy [Budoff 2008; Meijboom 2008; Miller 2008; Schroeder 2008; Stein 2008; Plass 2009]. Positron emission tomography (PET) allows quantitative regional and global assessment of myocardial blood flow (MBF) and coronary flow reserve (CFR) [Herzog 2009] and is an established gold standard for assessing myocardial ischemia. PET yields greater accuracy for evaluating the presence and location of coronary stenoses, compared with single-photon emission CT (SPECT) [Tamaki 1988; Go 1990; Steward 1991].

The integration of the 2 imaging modalities of CT and PET by image fusion into hybrid images that include the assessment of CFR has opened new opportunities for comprehensive structural and functional evaluation of CAD [Namdar 2005].

The aim of this study was to assess whether the use of hybrid imaging using PET and dual-source CT (DSCT) would lead to different or optimized decision-making with regard to surgical revascularization of target vessels, compared with the standard of care, which is currently based on anatomic information derived from coronary angiography.

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METHODS

Patients and Demographics

We enrolled 27 patients in this study (21 men and 6 women; mean ± SD age, 66 ± 10 years). Patients with an allergy to iodinated contrast media, an impaired renal function (serum creatinine >150 µmol/L), indications for urgent coronary artery bypass grafting (CABG) surgery, or previous coronary interventions (PCI/CABG) were excluded. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all patients.

Preoperative risk stratification revealed a mean EuroSCORE for the cohort of 3.8 ± 2.6. The patient demographics are summarized in Table 1.

CT Scan Protocol and Data Analysis

All patients were scanned with a DSCT system (SOMATOM Definition; Siemens Healthcare, Forchheim, Germany). After an initial nonenhanced scan for calcium scoring, patients received a single 2.5-mg dose of isosorbide dinitrate (Isoket; Schwarz Pharma, Monheim, Germany) and 80 mL of contrast agent (Ultravist 370, 370 mg/mL; Bayer Schering Pharma, Berlin, Germany). Besides the standard scanning parameters [Plass 2009], electrocardiography pulsing was used in all patients to reduce the radiation dose.

We assessed 15 coronary segments on the basis of modifications of the American Heart Association model of the coronary tree [Austen 1975]. All diameter measurements were performed with an electronic caliper tool. Coronary segments were assessed for the presence of morphologically significant stenoses, which were defined as a narrowing in the luminal diameter of >70%. Plaques were rated as calcified, noncalcified, or mixed.

PET Scan Protocol and Data Analysis

PET Images were acquired in 2-dimensional mode, either on a GE Advance PET/CT scanner or on a Discovery (LS/RX) PET/CT scanner (both GE Healthcare, Milwaukee, WI, USA). All patients received a 700- to 900-MBq injection of [^{13}N]ammonia into a peripheral vein prior to dynamic list-mode acquisition of emission data (nine 10-second, six 15-second, three 20-second, two 30-second, and one 900-second frames). A low-dose CT scan was obtained for attenuation correction (140 kV; 120-150 mA; slice thickness, 3.75-4.75 mm) [Koepfli 2004]. MBF was measured at rest and during standard pharmacologic stress (ie, a 7-minute infusion of adenosine at 0.14 mg/min per kilogram body weight) [Cerqueira 1994].

PET images were reconstructed with filtered back projection and reformatted into short-axis slices, as well as vertical and horizontal long-axis slices, of the left ventricle. Assessment of myocardial perfusion was based on the consensus of 2 experienced readers of the last 900-second frame, according to the 17-segment model and the semiquantitative scoring system of defect severity and extent recommended by the American Society of Nuclear Cardiology [Machac 2006] (Figure 1). In our study, a scan was considered in the categories of normal, ischemia, and fixed defect (scar).

Quantitative MBF was calculated from the dynamic frames via pixel-wise kinetic modeling with the PMOD software package (PMOD Technologies, Zurich, Switzerland) as previously reported [Wyss 2003]. CFR was calculated as the ratio of the hyperemic MBF to the resting MBF, and a CFR value >2.0 was considered normal [Herzog 2009]. The CFR values of the 17 segments were assigned to the 3 coronary territories according to a standardized myocardial segmentation model [Cerqueira 2002]. Territories with perfusion defects and subtended by stenotic coronary vessels were categorized as CAD territories; other segments were classified as remote. The mean regional CFR was assessed for CAD and remote segments.

PET and CT Fusion Protocol and Data Analysis

PET data were fused with DSCT data on a workstation (Advantage Workstation 4.4; GE Healthcare) by using the CardIQ Fusion software package (GE Healthcare) as

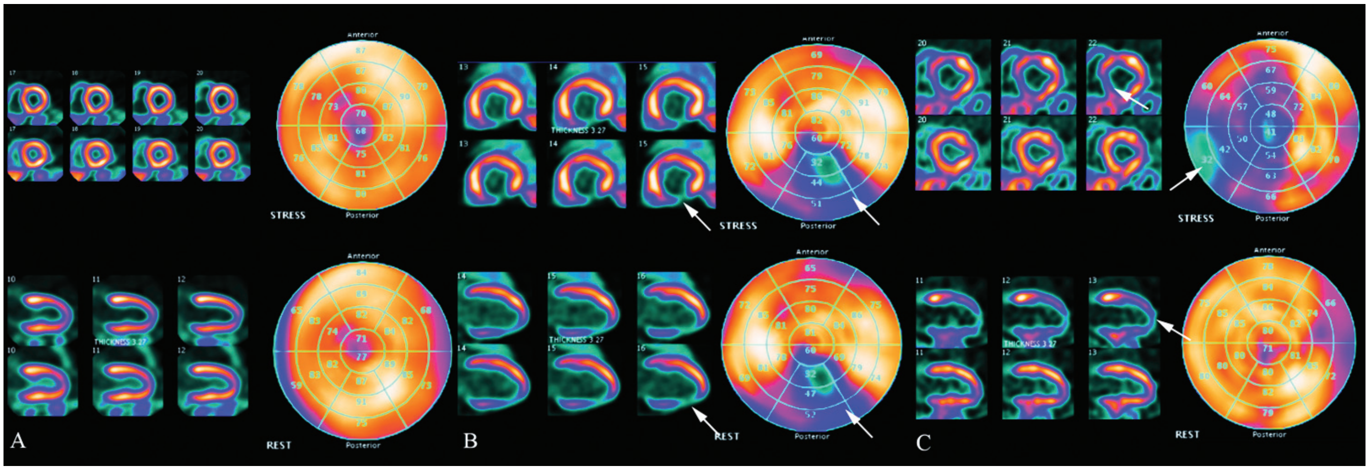

Figure 1. Perfusion images (short-axis longitudinal, long-axis, and polar plots) used in the clinical routine showing normal perfusion (A), fixed inferior perfusion defect inferior, ie, scar (B) (arrows), and reversible inferoseptal perfusion defect, ie, ischemia (C) (arrows).

previously validated [Gaemperli 2007a] to obtain hybrid images with the perfusion information overlaying the 3-dimensional volume–rendered CT images [Gaemperli 2007a] (Figure 2).

The data of the fused images were analyzed for the relationship between significant stenoses of the left anterior descending coronary artery (LAD), the circumflex branch (CX), and the right coronary artery (RCA), as well as myocardial perfusion defects in their respective territories, as previously reported [Gaemperli 2007b].

Catheter Coronary Angiography and Data Analysis

ICA was performed according to standard techniques, and at least 2 views in different planes were obtained for each coronary artery. The multiple views were recorded on a CD-ROM, and 2 cardiac surgeons who were aware of the

Table 1. Preoperative Demographics*

Parameter	Patients (n = 27)
Age, y	66 ± 10
EuroSCORE (standard)	3.8 ± 2.6
Ejection fraction	58% ± 13%
Obesity (BMI), n	16 (59%)
History of smoking, n	14 (52%)
Hyperlipidemia, n	15 (56%)
Diabetes, n	7 (26%)
Hypertension, n	21 (78%)
PAD, n	3 (11%)
COPD,	3 (11%)
NYHA class, n	
I	6 (22%)
II	10 (37%)
III	8 (30%)
IV	3 (11%)
CCS class, n	
I	10 (37%)
II	9 (33%)
III	7 (26%)
IV	1 (4%)
Myocardial infarction, n	
<90 d	4 (15%)
>90 d	5 (19%)
CABG, n	18 (67%)
Valve procedure, n	3 (11%)
CABG + valve procedure, n	6 (22%)

*Data are expressed as the mean ± SD where indicated. BMI indicates body mass index; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; CABG, coronary artery bypass grafting.

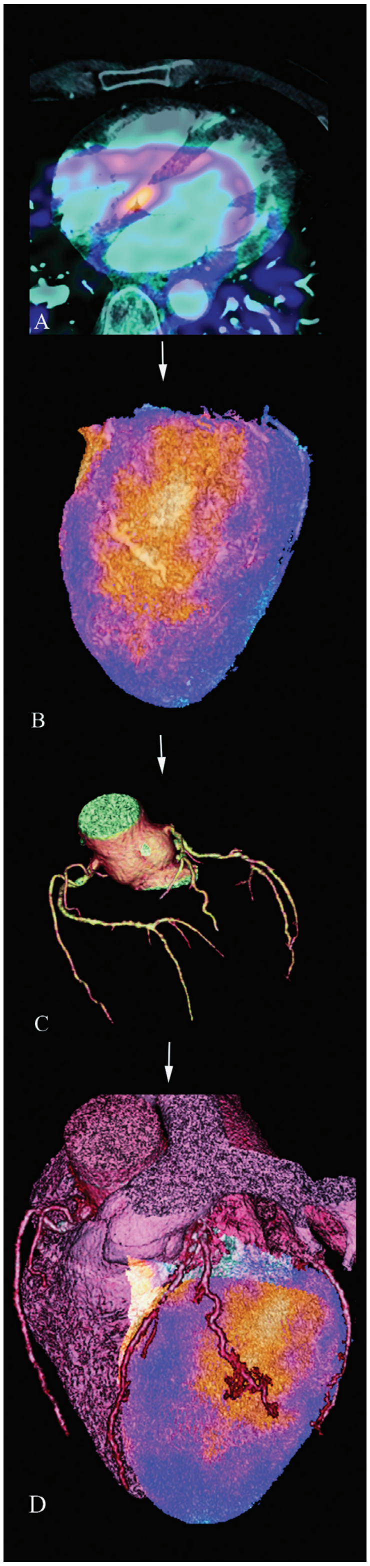

Figure 2. Fusion technique step by step: alignment between dual-source computed tomography and perfusion (A), definition of epicardium and vessels (B, C), and performance of the fusion of both information sources (morphology and function) (D).

patients' clinical history but were blinded to the CT results analyzed the images with regard to the presence of significant stenoses (defined as a luminal reduction of >70%) or their absence. Coronary artery segments with diameters as large as 1.5 mm were defined according to the scheme of the American Heart Association [Austen 1975].

The data were used as a "gold standard" and compared with the CT assessment for accuracy. The fractional flow reserve (FFR) was not routinely used in our catheterization laboratory. Preoperative stress tests, such as performed via echocardiography, were not performed standardly in all patients. When this information was acquired, it was used only for general decision-making with respect to the necessity for CABG; it was not used for making specific strategic surgical decisions.

Imaging Analysis Compared with Surgery

ICA results were assessed by cardiologists, CT coronary angiography (CTCA) results were assessed by radiologists, and PET results were evaluated by nuclear medicine physicians. The different specialists were not aware of the results of the other examinations. All assessments involved a cardiac surgeon who was not performing the surgery. After the preoperative imaging analyses were performed, the viability of the myocardium was analyzed for normal perfusion, ischemia, and scar differentiated to the LAD (including the diagonal branch), the CX (including the posterolateral branch), and the RCA (including the posterior descending artery) regions. These results were related to the locations of the distal anastomoses, and these imaging results were not known to the surgeons who performed the operation. In addition, we made calculations of the CFR in these regions that differentiated between normal (>2) and ischemia (<2). After the surgery was performed, these preoperatively assessed CFR data and the presence or absence of ischemia were correlated to the different bypass grafts and the affected regions.

Statistical Analysis

The location and number of significant stenoses were documented and compared with the ICA results as the standard of reference. The diagnostic accuracy of CT versus ICA was calculated according to a segment-based analysis. A patient-based analysis was also performed. This analysis included all patients, with censoring of any nonevaluative coronary segment by CT as a false positive, because every patient with nonevaluable segments would undergo ICA in clinical practice. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated from 2 2 contingency tables. Data for quantitative variables were summarized as the mean ± SD, and data for categorical variables were expressed as frequencies or percentages.

RESULTS

Sixty-seven percent of all patients underwent isolated CABG. Combined CABG and valve surgery (2 mechanical aortic valves, 3 biological aortic valves, 1 mitral valve reconstruction) was performed in 22% of the patients, and isolated valve surgery (2 biological aortic valve replacements, 1 biological double aortic and mitral valve replacement) was performed in 11% (3/27) of the patients. A total of 56 bypass grafts (28 venous grafts, 25 internal mammary artery grafts, 3 radial artery grafts) and 66 distal anastomoses were placed.

In 22 of the 27 patients, it was possible to perform the complete protocol for both imaging modalities (DSCT and PET), including the fusion imaging (Figure 3). The PET imaging had to be cancelled in 2 patients (because of the patient's claustrophobia in 1 case and because of a bronchial spasm during adenosine stress in the other). DSCT was not performed in 2 patients for logistical reasons. All other scans were conducted on the same day without complications. The results of these assessments were withheld from the surgeon at the time of surgery.

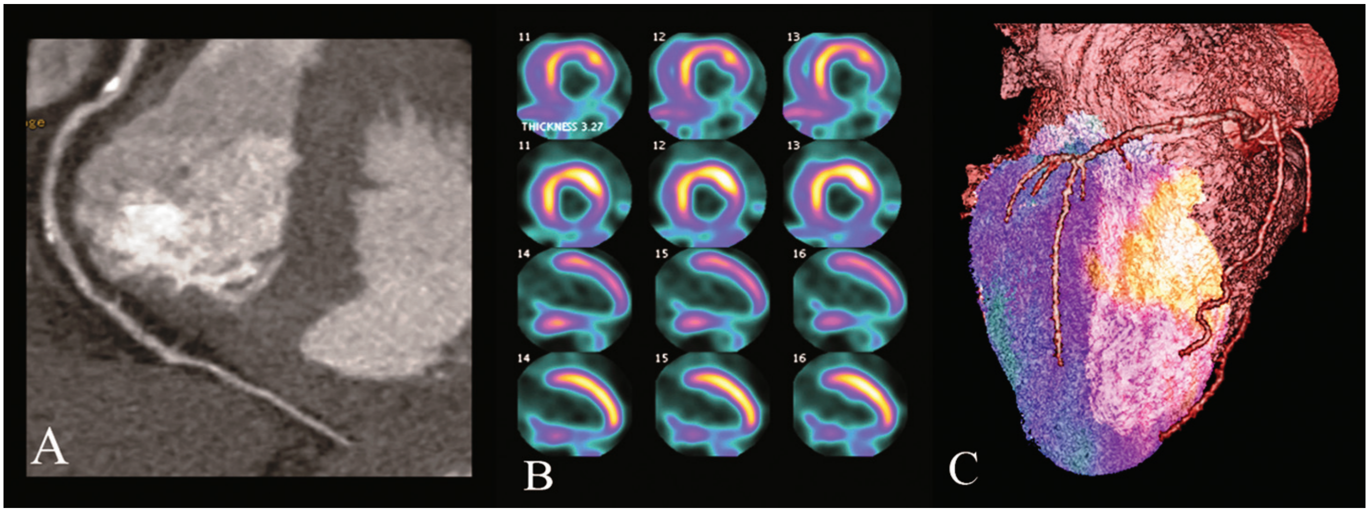

Figure 3. Dual-source computed tomography image showing significant stenosis in the proximal right coronary artery (RCA) (A), positron emission tomography images showing an inferior perfusion defect in the distal RCA (B), and fusion images showing that the lesion in the RCA is causing the inferior perfusion defect (C).

Dual-Source CT

For 25 (93%) of the 27 patients, we assessed a total of 375 coronary segments by DSCT and ICA. The DSCT analysis showed 93% concordance (66/71) with the ICA analysis with respect to significant stenoses. Two segments were nonevaluable, 5 stenoses were not detected in the DSCT evaluation, and 2 significant stenoses in DSCT were not rated to be significant in the ICA analysis. The sensitivity, the specificity, the positive predictive value, and the negative predictive value were 93.1%, 98.7%, 94.4%, and 98.4%, respectively. Plaque composition was characterized as noncalcified in 21% of the cases, calcified in 46%, and mixed in 33%.

Positron Emission Tomography

In 89% (24) of the 27 patients, PET was performed to assess potential ischemia and/or scar in the regions of the LAD, CX, and RCA. CFR was calculated in 78% (21) of the 27 patients.

The PET evaluation showed 1 ischemic region in 16 patients, with 11 of these 16 patients showing >1 ischemic region. At least 1 region with scar was identified in 12 patients. Of these patients, 5 had regions with both a scar and ischemia. One patient had no ischemia and no scar.

PET/CT Fusion

In 91% (60) of the 66 distal anastomoses, the specific myocardial region could be assessed by PET/DSCT fusion imaging for significant stenosis and ischemia. Forty-eight percent (29/60) of the distal anastomoses were placed to significantly stenosed coronaries with concordantly assessed preoperative ischemic myocardium (13 to the LAD, 7 to the CX, and 9 to the RCA), 14% (8/60) of the distal anastomoses served myocardial territories with fixed perfusion defects (scar), and 38% (23/60) of the bypass grafts served nonischemic myocardium.

The preoperative CFR was obtained for 95% of the bypassed myocardial regions. The mean CFR value was 1.7 ± 0.5 for the entire heart, whereas the mean CFR was 1.7 ± 0.5 for the LAD territory, 1.6 ± 0.3 for the RCA territory, and 1.9 ± 0.5 for the CX territory. None of the patients had a CFR >2 in all 3 main territories (ie, LAD,CX, and RCA), 6 patients had a CFR >2 in 2 territories, and 3 patients had a CFR >2 in 1 territory. Eighty-six percent (25/29) of the revascularized ischemic segments had a preoperative CFR <2. Similarly, 78% (18/23) of those segments that were revascularized despite a lack of stress-induced ischemia had a CFR <2.

Table 2 summarizes the correlation of the preoperatively assessed CFR (myocardial perfusion defects) with the bypassed territories.

DISCUSSION

This study demonstrates the potential clinical impact of preoperative hybrid cardiac imaging via fusion of 2 imaging modalities—DSCT and myocardial PET perfusion imaging—in patients undergoing cardiac surgical procedures. Hybrid cardiac imaging allows comprehensive evaluation of ischemic heart disease, because it not only documents the anatomic information of coronary lesion severity but also provides information on its hemodynamic relevance. Specific software enables rapid offline fusion of CT and nuclear myocardial perfusion images, making its use feasible in the clinical routine [Gaemperli 2007b]. The added value of hybrid imaging over side-by-side analysis is based on the fact that hybrid imaging allows accurate and intuitive assignment of any ischemic myocardial territory to the stenotic lesion of its feeding coronary vessel [Namdar 2005; Gaemperli 2008].

Table 2. Correlation of the Preoperatively Assessed Coronary Flow Reserve (CFR) (Myocardial Perfusion Defects) and the Bypassed Territories

CFR	No Ischemia	Ischemia	Scar
<2	32% (18/57)	44% (25/57)	5% (3/57)
>2	9% (5/57)	6% (4/57)	4% (2/57)

In this study, the results of the preoperative PET/CT images (which were unknown to the surgeon) were related to the surgical procedures performed. We found that 49% of coronary vessels were grafted despite a lack of flow-limiting stenosis according to the noninvasive imaging analysis, although a substantial fraction of these vessels had a CFR <2, which might have served as a justification for the intervention. The discrepancy between the selection of target vessels by the surgeon based on a review of angiographic data and that based on an image-guided approach using functional imaging underscores the potential role for hybrid imaging in the decision-making process for revascularization procedures. This approach would contribute to ascertaining the appropriate selection of target vessels for revascularization. By doing so, approximately half of the unnecessary grafts would not have been made in our study population, and none of the appropriate revascularizations would have been falsely withheld.

In order to integrate cardiac hybrid imaging into the decision-making process of cardiac surgeons, it is important that the imaging information be appropriately transferred from the workstation (where the hybrid pictures are generated) into the operating room. In fact, an added clinical value of hybrid imaging can be anticipated only if the added information leads to consequences in the treatment strategy and, ultimately, to an improved outcome.

Nevertheless, the present findings do not necessarily imply that the standard of care provided by cardiac surgeons in the daily clinical routine has been wrong ever since CABG was introduced. First, grafting despite a lack of ischemia might by justified by the role of the poststenotic collaterals for perfusion into adjacent territories. Second, the impact of the different plaque qualities—irrespective of their hemodynamic relevance—in a preventive revascularization strategy with CABG remains to be elucidated, because bridging may prevent acute life-threatening myocardial infarction caused by the rupture of a nonstenotic plaque [Narula 2008; Tahara 2009]. At present, however, accurately predicting vulnerability and, ultimately, plaque rupture remains very difficult.

Therefore, a substantial number of bypass grafts are placed for "prognostic" reasons. This practice is driven by the fact that an anatomically significant stenosis may be documented even though the presence of ischemia may be uncertain. With this rationale, more than half of the grafts placed to nonischemic areas in our study might have been justified, although more-precise data would be needed to define the prognostic impact. CFR has also been evaluated, and it might be helpful as an additional tool for decision-making in CABG, especially if the CFR is <2 and no ischemia is apparent. In fact, a CFR value <2 has recently been found to predict an adverse outcome, despite PET evidence of normal perfusion [Herzog 2009]. We found, coincidentally, that PET results revealed a CFR <2 in 78% of the regions with an anastomosis placed to nonischemic myocardium, suggesting that bypass grafts to these territories have the potential to produce a beneficial long-term prognostic impact. Thus, in the process of decision-making for an optimal treatment strategy, the diagnosis of ischemia should be complemented by a CFR assessment. This recommendation is in line with recent findings of the FAME trial [Tonino 2009], which showed that per-lesion ischemia-driven revascularization improved outcomes.

There is ongoing debate regarding the best revascularization strategy, ie, an ample strategy ("the more the better") versus revascularization confined to significant lesions serving ischemic territories ("the less the better"). The higher closure rate of bypass grafts in postoperative follow-up studies of patients with 4 anastomoses compared with <4 bypass grafts suggests that ample revascularization may lead to "exaggerated" revascularization that remains clinically irrelevant [Magee 2008].

On the other hand, more relevant in CABG is not to miss important ischemic areas, because incomplete revascularization has been shown to produce a higher postoperative rate of major adverse cerebral or cardiac adverse events and therefore should be avoided [Bucher 2000; Ong 2006]. It is foreseeable that the use of fused imaging with detailed information on the location of a lesion and the consequent ischemic territory might also facilitate choosing a hybrid revascularization approach, eg, with a left internal mammary artery bypass to the LAD and stenting of an isolated stenosis, thereby avoiding a sternotomy. Such choices may improve outcome and patient satisfaction.

Although multislice CT is often used as a noninvasive imaging tool to exclude CAD, most cardiac surgeons do not yet consider this technique sufficiently mature to rely on it entirely for decision-making for or preoperative planning of CABG procedures. Therefore, coronary angiography has remained the tool of first choice for preoperative evaluation. Of course, cardiovascular specialists are able to correlate ICA results with perfusion defects observed with PET, but the goal of fusing the CT and PET diagnostic imaging modalities is to optimize the techniques already available. To use a completely noninvasive approach that has no procedure-related morbidity and mortality has lower costs than catheter angiography and is associated with equal or even lower radiation doses compared with ICA, when the appropriate protocols are used. Furthermore, we believe that this hybrid approach allows the most exact mapping of a stenosis and its corresponding ischemic region, which may be illustrated objectively on imaging media without reliance on an individual's estimation from a side-by-side analysis.

This superiority over a side-by-side analysis may be due, at least in part, to the fact that 3-dimensional hybrid imaging provides additional information about the hemodynamic relevance of the lesion and facilitates interpretation of the lesion by allowing an exact allocation of the perfusion defects to its subtending coronary artery. This information cannot be obtained reliably via mentally integrating CTCA and SPECT myocardial perfusion imaging results side by side, because standard myocardial distribution territories correspond with the real anatomic coronary tree only 50% to 60% of the time [Schindler 1999]. The more detailed an assessment of an ischemic region one can obtain, the better one can decide if and where a bypass graft should be placed.

Limitations

The main limitation of this study is the limited number of patients in this study. This limitation was due, however, to the pilot nature of the study. Consequently, the study was not designed to assess clinical outcome, because the aim was a proof of concept. In fact, the results support a potential role for hybrid imaging as a gatekeeper before cardiac surgery, in line with previous evidence for such a role prior to catheter-based revascularization [Gaemperli 2009]. Furthermore, we did not use the most recent radiation dose–saving CT protocols, which produce effective radiation doses of approximately 1 to 4 mSv for CTCA of the entire chest [Leschka 2009; Alkadhi 2010]. In addition, many cardiovascular surgeons still do not have experience with using the complete imaging media and working at the dedicated workstation. That, however, should not be a reason not to move forward with new imaging technologies and their various combinations. The goal for the cardiovascular surgeon should be to actively become familiar with these techniques so as to achieve an optimal interdisciplinary work flow.

Finally, the invasive angiographic classification of coronary lesions as significant was not complemented by a functional assessment, such as FFR. However, the latter had not yet been implemented into our daily routine during the study, which was completed before the solid data of Tonino et al [2009] became available and before FFR was adopted in the latest European Society of Cardiology guidelines for revascularization [Wijns 2010]. In fact, recognition of this need has also contributed to a continuing increase in the use of FFR in our catheterization laboratory; however, the present study was conducted before the release of the aforementioned study and the results of the FAME trial. Unfortunately, at that time, FFR was not used as a routine tool in our catheterization laboratory, which is why it was not available for our patients.

CONCLUSION

The use of noninvasive hybrid cardiac imaging combining CTCA with PET prior to coronary revascularization is a technically established method that may help surgeons to fully incorporate clinical evidence into their decision-making for selecting target vessels. Prospective trials are now needed to prove the feasibility of the transfer of all information to the cardiac surgeon before a specific therapeutic step is taken. Only when the outcomes obtained with these new modalities prove to be superior will more elaborate preoperative assessments be justified.

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