Corrected coronary opacification decrease from coronary computed tomography angiography: Validation with quantitative 13N-ammonia positron emission tomography

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Received Mar 25, 2017; accepted Jun 7, 2017
doi:10.1007/s12350-017-0980-2

Background. **To assess the functional relevance of a coronary artery stenosis, corrected coronary opacification (CCO) decrease derived from coronary computed tomography angiography (CCTA) has been proposed. The present study aims at validating CCO decrease with quantitative 13N-ammonia positron emission tomography (PET) myocardial perfusion imaging (MPI).**

Methods and Results. **This retrospective study consists of 39 patients who underwent hybrid CCTA/PET-MPI. From CCTA, attenuation in the coronary lumen was measured before and after a stenosis and corrected to the aorta to calculate CCO and its decrease. Relative flow reserve (RFR) was calculated by dividing the stress myocardial blood flow (MBF) of a vessel territory subtended by a stenotic coronary by the stress MBF of the reference territories without stenoses. RFR was abnormal in 11 vessel territories (27%). CCO decrease yielded a sensitivity, specificity, negative predictive value, positive predictive value, and accuracy for prediction of an abnormal RFR of 73%, 70%, 88%, 47%, and 70%, respectively.**

Conclusions. **CCTA-derived CCO decrease has moderate diagnostic accuracy to predict an abnormal RFR in PET-MPI. However, its high negative predictive value to rule out functional relevance of a given lesion may confer clinical implications in the diagnostic work-up of patients with a coronary stenosis. (J Nucl Cardiol 2019;26:561–8.)**

Key Words: Corrected coronary opacification • quantitative PET myocardial perfusion imaging • relative flow reserve

See related editorial, pp. 569–573

Electronic supplementary material The online version of this article (doi:10.1007/s12350-017-0980-2) contains supplementary material, which is available to authorized users.

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1071-3581/$34.00

Abbreviations

CCO	Corrected coronary opacification
CCTA	Coronary computed tomography angiography
SPECT	Single photon emission computed tomography
PET	Positron emission tomography
RFR	Relative flow reserve
MBF	Myocardial blood flow
CFR	Coronary flow reserve
TAC	Time-activity curves
ICA	Invasive coronary angiography
PCI	Percutaneous coronary intervention

INTRODUCTION

Low-dose coronary computed tomography angiography (CCTA) is a valuable non-invasive tool to assess coronary artery disease (CAD) with high negative predictive value[1] and to guide subsequent treatment strategies.[2,3] A limitation of CCTA is its moderate performance in assessing the functional relevance of a coronary stenosis as is inherently true for any anatomic test.[4] However, proof of functional relevance of a stenosis prior to any revascularization procedure is mandatory to improve outcome.[5–7] Consequently, combining anatomic information on the coronary arteries derived from CCTA with functional information from single photon emission computed tomography (SPECT) or positron emission tomography (PET) myocardial perfusion imaging (MPI) either side-by-side or fused as hybrid imaging was established and has been shown to offer added clinical and prognostic value.[8–10] Concurrently, there is growing interest in parameters derived directly from CCTA to assess the functional relevance of a coronary lesion. Fractional flow reserve from CCTA (FFR_{CT}) has been introduced recently and several prospective trials have lent support to suggest a clinical role.[11,12] Calculation of FFR_{CT}, however, currently remains a complex and cumbersome process with limited availability, but easily and quickly derivable parameters such as the transluminal attenuation gradient (TAG)[13,14] and the decrease in corrected coronary opacification (CCO)[15–17] have emerged as promising alternatives. While TAG may be more related to vessel diameter than to stenosis severity,[18] CCO decrease has consistently yielded high diagnostic accuracy (79 to 89%) to predict functional relevance of a coronary stenosis.[15–17] It has, nevertheless, not yet been investigated in comparison to quantitative PET-MPI which is considered the gold standard for myocardial perfusion assessment.[19–21] Moreover, the calculation of relative flow reserve (RFR) from PET-MPI has not only served as the standard of reference for the validation of invasive FFR,[22] but has also been shown in some patient populations to yield significantly higher diagnostic accuracy than stress myocardial blood flow (MBF) or coronary flow reserve (CFR).[23] The aim of the present study was to validate CCO decrease with stress MBF in PET-MPI and to assess the accuracy of CCO decrease to predict an abnormal RFR as derived from the gold standard PET-MPI.

METHODS

Study Population

We retrospectively identified 67 patients who underwent hybrid CCTA/PET-MPI at our institution due to known or suspected CAD. Exclusion criteria were history of coronary artery bypass surgery and patients who suffered any events between the CCTA and the PET scan. The study protocol was approved by the institutional review board (cantonal ethics committee, BASEC-Nr. 2016-00177) and informed consent was waived for all patients scanned before 2014. For all patients scanned afterwards, written informed consent was obtained. No funding was obtained for performing this study.

CCTA Acquisition and Assessment of CCO Decrease

Patients underwent contrast-enhanced CCTA on either a 64-slice scanner ($n = 39$; LightSpeed VCT or Discovery HD 750, both GE Healthcare, Waukesha, WI, USA) or a 256-slice scanner ($n = 28$; Revolution CT, GE Healthcare) using helical ($n = 4$) or axial scanning with prospective ECG-triggering ($n = 63$) as previously described.[24,25] Bolus tracking was performed and image acquisition was started 4 seconds after the signal density reached a predefined (i.e. 120 Hounsfield units) or a visually detectable threshold in the ascending aorta. In order to achieve a target heart rate <65 bpm, intravenous metoprolol (5-30 mg) was administered prior to scanning if necessary. Furthermore, all patients received 2.5 mg sublingual isosorbide dinitrate 2 minutes prior to the scan.

CCO decrease was measured for each coronary stenosis (i.e. luminal diameter narrowing ≥50%) as previously described.[15] In brief, a region of interest (ROI) with a diameter of 1 mm was placed in the center of the coronary lumen and a ROI with a diameter of 10 mm was placed in the descending aorta on the same axial slice. CCO was calculated as the ratio of mean attenuation in the coronary ROI over the aortic ROI. CCO was measured twice as close as possible to the stenosis and due care was taken to avoid calcifications and streak artifacts in the measurements and the lower values were used to calculate CCO decrease as the difference of proximal minus distal value.

PET Acquisition and RFR Calculation

Patients underwent ^{13}N-ammonia PET at rest and during adenosine stress at a standard rate (0.14 mg/min/kg) over 7 minutes with 700-900 MBq of ^{13}N-ammonia administered intravenously into a peripheral vein after 3 minutes into stress. Images were acquired either on a Discovery (LS/RX) PET/CT scanner or on an Advance PET scanner (both GE Healthcare), as previously reported in detail.[19]

Quantitative MBF and CFR were calculated using the commercially available PMOD software (version 3.7; PMOD Technologies Ltd., Zurich, Switzerland) developed and validated at our institution.[26] In brief, a volume of interest (VOI) encompassing the left ventricular myocardium was drawn and two more VOIs were put into the blood pool of the left and right ventricle. Myocardial and blood-pool time-activity curves (TAC) were obtained from dynamic frames corrected for radioisotope decay. Stress and rest MBF was estimated by model fitting of the blood pool and myocardial TACs corrected for spill-over and partial volume.[19] CFR was calculated as the ratio of stress MBF over rest MBF.

Considering that standard vascular territory distribution in myocardial perfusion interpretation may be subject to a substantial morphologic variability of the coronary tree,[27] quantitative PET datasets (using a 17-segment model) were fused with CCTA using a commercially available software (CardIQ Fusion, GE Healthcare) in order to assure true co-registration. For each coronary artery, mean MBF of the two myocardial PET segments subtended by the most distal vessel section was recorded and allocated to this coronary artery.[10] Subsequently, in a subgroup of patients with 1- or 2-vessel-disease, relative flow reserve (RFR) was calculated by dividing the MBF of a coronary artery with a stenosis by the mean MBF in the reference vessel(s) without a coronary stenosis. An RFR below 0.69 was considered abnormal.[28]

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR) if data was not normally distributed, and categorical variables as percentages. Kolmogorov–Smirnov test was applied to assess normal distribution. Comparison of continuous variables with non-normal distributions between groups was performed with Mann–Whitney U and Kruskal–Wallis test. Spearman's correlation was used to measure the association between CCO decrease and stress MBF. Receiver-operating characteristics (ROC) curve analysis was plotted to illustrate the performance of CCO decrease to diagnose an abnormal RFR. Youden's index was calculated to define the optimal threshold. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CCO decrease were calculated on a per-vessel basis, whereby an abnormal RFR served as the standard of reference for hemodynamic relevance. A P value $<.05$ was considered statistically significant. SPSS version 20.0 (IBM Corporation, Armonk, NY, USA) was used for analysis.

RESULTS

Study Population

The baseline characteristics of the study population ($n = 67$) are summarized in Table 1. Twenty-seven patients (40%) were referred for exclusion of CAD and 40 (60%) for evaluation of known CAD. Twenty-one patients (53%) had a stent and 16 (40%) a history of prior myocardial infarction. Figure 1 depicts screening, inclusion, and eligibility for analysis of the study population in a flow chart.

CCTA Findings

CCTA ruled out CAD in 26 patients (39%). In 41 patients (61%), 99 stenoses were documented in a total of 73 vessels resulting in 18 patients with one-vessel, 14 patients with two-vessel, and 9 patients with three-vessel-disease. CCO decrease was successfully measured across each stenosis and varied significantly by stenosis severity ($P < .001$) as illustrated in Figure 2.

PET Findings

Rest and stress MBF as well as CFR differed significantly across different stenosis severities ($P < .05$; Table 2). Among the vessels with a coronary stenosis, median stress MBF was 1.41 mL/min/g (IQR,

Table 1. Patient baseline characteristics ($n = 67$)

Male gender, *n* (%)	53 (79)
Age, years	
Mean ± Standard deviation	62 ± 11
Range	26-83
Body mass index, kg/m^2	
Median (interquartile range)	26.8 (24.1-30.0)
Range	19.4-48.9
Cardiovascular risk factors, *n* (%)	
Smoking	38 (57)
Diabetes mellitus	12 (18)
Hypertension	42 (63)
Dyslipidemia	37 (55)
Positive family history	25 (37)
Clinical symptoms, n (%)	
Typical angina	14 (21)
Atypical chest pain	18 (27)
Dyspnoea	10 (15)
Other (i.e. palpitations, fatigue)	3 (5)
Asymptomatic	18 (27)
Unknown	4 (6)

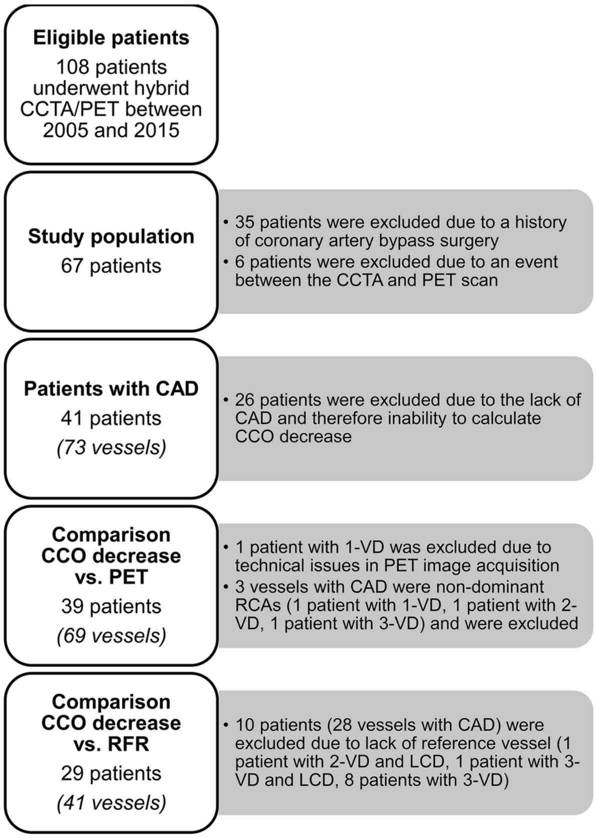

Figure 1. The flow chart depicts screening, inclusion, and eligibility for analysis of the study population.

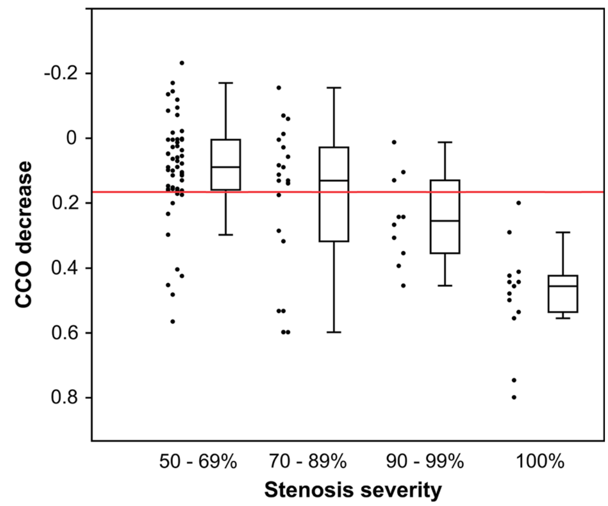

Figure 2. Box-and-whisker plot showing corrected coronary opacification (CCO) decrease of all lesions for subsets of anatomic stenosis severity (50% to 69%, 70% to 89%, 90% to 99%, and 100% diameter narrowing). The *red horizontal line* corresponds to the cut-off value for an abnormal CCO decrease as defined in the present study (CCO decrease >0.166). The *boxes* represent the interquartile range (IQR) and the *dark line* within each *box* indicates the median. The whiskers are defined as 1.5 times the IQR.

0.87 to 1.75 mL/min/g). In the subgroup of patients with 1- or 2-vessel-disease, RFR was calculated in 41 vessels with a coronary stenosis and resulted in a median of 0.84 (IQR, 0.66 to 1.13). RFR was abnormal in 11 patients (27%).

Diagnostic Accuracy of CCO Decrease

Stress MBF correlated significantly with CCO decrease ($r = -0.480$; $P < .001$; Figure 3).

The ROC curve analysis for CCO decrease to diagnose an abnormal RFR resulted in an AUC of 0.712 ($P < .05$; Figure 4). Youden's index was calculated and identified the optimal cut-off of CCO decrease at 0.166. Implementing the latter, median RFR was significantly lower in vessels with an abnormal CCO decrease compared to vessels with a normal CCO decrease (0.69 vs. 1.02; $P < .05$; Figure 5). An abnormal CCO decrease correctly detected an abnormal RFR in 8 of 11 vessels and correctly ruled out an abnormal RFR in 21 of 30 vessels. This resulted in a sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of 73% (95% CI: 39% to 94%), 70% (95% CI: 51% to 85%), 88% (95% CI: 68% to 97%), and 47% (95% CI: 23% to 72%) and 70%, respectively (Table 3).

Implementing a threshold of 0.166 for an abnormal CCO decrease, stress MBF was significantly lower in vessels with an abnormal CCO decrease compared to vessels with a normal CCO decrease (1.04 mL/min/g vs. 1.70 mL/min/g; $P < .001$).

DISCUSSION

The present study is the first to compare CCO decrease with stress MBF and to report on its ability to predict abnormal RFR in vessels with a coronary stenosis. Our results demonstrate that CCO decrease correlates with stress MBF and that the presence of an abnormal CCO decrease is associated with significantly lower RFR. Although the assessment of functional relevance of coronary stenoses by CCTA-derived CCO decrease has only moderate diagnostic accuracy, it excludes an abnormal RFR with high negative predictive value. Thus, assessment of CCO decrease from CCTA may confer clinical implications in the diagnostic work-up of patients with a coronary stenosis. While some studies have previously reported high diagnostic accuracy of CCO decrease in comparison to TIMI flow, magnetic resonance MPI, or invasive FFR,[15–17] it has not yet been compared to PET-MPI, the current gold standard for quantitative MBF assessment. Compared to

Table 2. MBF and CFR stratified by stenosis severity

	<50% (*n* = 53)	50–69% (*n* = 30)	70–89% (*n* = 18)	90–99% (*n* = 9)	100% (*n* = 10)	*P* value
Stress MBF (mL/min/g)	1.95 (1.34–2.46)	1.68 (1.36–2.11)	1.46 (1.12–1.64)	0.62 (0.54–1.81)	0.87 (0.74–1.20)	$P < .001$
Rest MBF (mL/min/g)	0.78 (0.65–0.96)	0.80 (0.68–0.90)	0.71 (0.60–0.79)	0.59 (0.46–1.03)	0.65 (0.57–0.72)	$P < .05$
CFR	2.29 (1.87–3.03)	2.04 (1.60–2.53)	2.02 (1.53–2.34)	1.19 (1.01–2.50)	1.42 (1.05–1.90)	$P < .001$

Values given are median (interquartile range).
MBF, Myocardial blood flow; *CFR*, Coronary flow reserve; *NA*, not applicable.

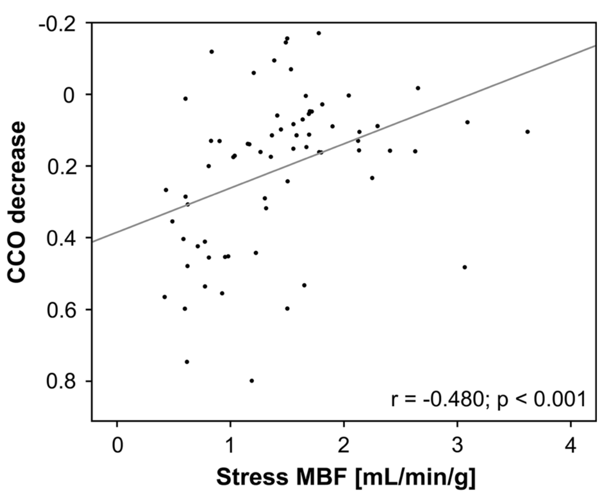

Figure 3. In vessels with a stenosis, stress MBF in the vascular territory correlates significantly with the CCO decrease across the stenosis ($r = -0.480$; $P < .001$).

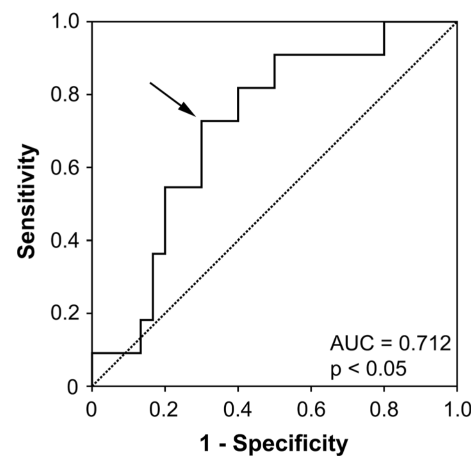

Figure 4. ROC curve analysis depicts an AUC for CCO decrease to predict an abnormal RFR of 0.712 ($P < .05$). The *arrow* indicates the optimal cut-off for CCO decrease at 0.166.

previous reports,[15–17] the lower diagnostic accuracy in the present study is most likely linked to the different standard of reference since the number of patients as well as the disease prevalence was comparable. Nonetheless, the results are consistent with these reports with regard to the high negative predictive value of CCO decrease.

It is well known that morphological stenosis severity poorly predicts functional relevance[4] although assessment of functional relevance is the key to appropriate clinical decision-making. In fact, deferral from revascularization in case of functionally relevant stenoses[29] as well as revascularization of non-relevant stenoses[5,30] both have been associated with less favorable outcomes in randomized trials. Consequently, current guidelines mandate complementing pure anatomical characterization of a coronary stenosis with functional assessment for evidence-based target lesion revascularization. Despite increasing evidence and the current guidelines, both non-invasive stress testing before invasive coronary angiography (ICA) and FFR before percutaneous coronary intervention (PCI) are underused in daily practice.[31,32] Furthermore, although it has been demonstrated that multimodality imaging successfully identifies patients at increased risk for adverse cardiovascular outcome and substantially reduces downstream resource utilization,[9,33–36] SPECT/CCTA and PET/CCTA are not yet widely adopted in clinical routine. The clinical implications of the present study lie in the ease of use of CCO decrease at no additional costs. The potential application of CCO decrease to predict abnormal RFR and thus offering functional assessment of a coronary stenosis may pave the way to individualize clinical workflow. Due to its moderate diagnostic accuracy CCO decrease may not replace MPI. However, thanks to the high negative

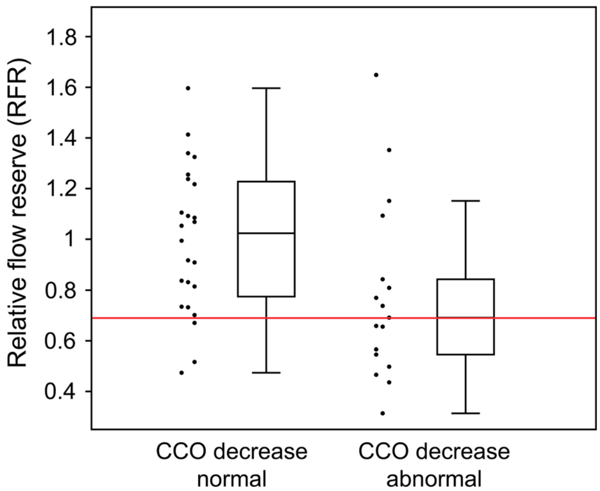

Figure 5. Box-and-whisker plot showing relative flow reserve (RFR) in vessels with either a normal or an abnormal CCO decrease. The *red horizontal line* corresponds to the cut-off value for an abnormal RFR as previously defined (RFR < 0.69).[28].

Table 3. Diagnostic accuracy of CCO decrease

Vessels with a stenosis, n	41
Abnormal RFR, *n*	11
True positive, *n*	8
False positive, *n*	9
True negative, *n*	21
False negative, *n*	3
Sensitivity, %	73 (39-94)
Specificity, %	70 (51-85)
Negative predictive value, %	88 (68-97)
Positive predictive value, %	47 (23-72)
Accuracy, %	70
Positive likelihood ratio	2.42
Negative likelihood ratio	0.39

predictive value to exclude functional relevance in intermediate stenoses, CCO decrease could potentially be endorsed as a gatekeeper after CCTA for additional non-invasive diagnostic work-up. If CCO decrease is normal, patients might be safely deferred from further testing such as MPI. On the contrary, if CCO decrease is abnormal, further non-invasive testing with SPECT or PET-MPI should be added and patient with ischemic burden above 10% of the left ventricle myocardium should be considered for revascularization.[7] Through this approach, downstream resource utilization may be influenced in a cost-effective manner and the probability for a comprehensive anatomic and functional non-invasive assessment before the patient is referred to invasive coronary angiography is increased.

We acknowledge the following limitations. First, our study design was retrospective and the patient population was rather small. Future studies should prospectively assess the role of CCO decrease in the clinical workflow. Second, MBF can be impaired in a variety of cardiovascular diseases and reduced stress MBF values by PET-MPI cannot discriminate between epicardial coronary obstruction or microcirculatory dysfunction. While a pathologic RFR may suggest epicardial CAD[23,28] a normal RFR in combination with a homogenous stress MBF reduction may result from either balanced ischemia due to epicardial multi-vessel CAD or microvascular disease. If the latter also interacts with CCO decrease values remains to be determined. However, since the CCO measurements are performed at low flow conditions and therefore do not depend on the vasodilatory capacity of the microvascular tree, this seems less likely. Third, although previous studies have demonstrated that intraluminal attenuation decreases with diminution of vessel diameter,[18] CCO decrease is not commonly corrected for vessel diameter. However, since CCO decrease is measured within 2 cm proximal and distal of a stenosis, a relevant impact of vessel diameter seems rather unlikely. Finally, due to the relative small sample size and due to the single-center retrospective nature of this study, any extrapolation of the CCO cut-off point to distinguish between stenoses with and without hemodynamic significance to any patient population substantially differing from the one studied here should be made only with caution.

In conclusion, CCTA-derived CCO decrease has moderate diagnostic accuracy to predict an abnormal RFR in PET-MPI. However, its high negative predictive value to rule out functional relevance of a given lesion may confer clinical implications in the diagnostic work-up of patients with a coronary stenosis.

NEW KNOWLEDGE GAINED

Due to the moderate diagnostic accuracy of CCO decrease, the use of more advanced imaging techniques to assess myocardial perfusion is indispensable. However, thanks to the high negative predictive value of CCO decrease it may be endorsed as a gatekeeper for implementation of a patient-tailored non-invasive further diagnostic work-up.

Acknowledgments

We thank Verena Weichselbaumer, Martina Vogt, Tania Lagrange, Lasien Vojo, and Kevin Frei for their excellent technical support.

Disclosure

The authors do not have any personal conflicts of interest to declare. However, the University Hospital Zurich holds a research agreement with GE Healthcare.

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