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Patterns of Opacification in Coronary CT Angiography: Contrast Differences and Gradients

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Abstract Iodinated contrast delivery is a key component of coronary computed tomography (CT) angiography. However, the purpose of contrast delivery has been limited to morphology alone. Specifically, iodine opacification of the coronary lumen has been used to separate it from the coronary artery wall and lesions within the coronary arteries. Because contrast is delivered to the coronary arteries according to the coronary blood flow, there is flow information encoded within the contrast opacification which, depending on CT hardware and acquisition protocol, can be recognized in coronary CT angiography. In addition, metrics related to flow have been identified and studied. They include coronary contrast opacification differences and contrast opacification gradients.

Keywords Coronary CT angiography · Coronary artery disease · Contrast opacification gradients · Contrast opacification differences

Introduction

Coronary computed tomography angiography (CTA) is an important noninvasive tool for the evaluation of suspected coronary artery disease (CAD) in stable patients. Its largest benefit to date has been the high negative predictive value when invasive coronary angiography (ICA) is used as a reference standard. However, computed tomography (CT) has lower specificity for predicting the functional significance of coronary lesions, a current role for other cardiac imaging modalities including nuclear or magnetic resonance methods. For CT, the reported positive predictive values vary widely between roughly 50 %–80 %, particularly in arteries with moderate (50 %–70 % diameter) stenosis [1]. Thus, a commonly used algorithm is to reserve CT for patients in whom a normal, or near-normal, study is likely. One example is a patient with atypical chest pain and a low pre-text likelihood of coronary artery stenoses. In such a patient, a normal CT scan provides reassurance. However, if the CT scan is abnormal, the patient will in fact have CAD, and the further workup will generally include cardiac imaging at stress. If ischemia is suspected the patient would then proceed to ICA with or without fractional flow reserve (FFR), potentially followed by intervention. Although it is well validated and accepted, this strategy is overall a less efficient utilization of resources than the development of a single imaging study that provides both anatomical and functional coronary assessment [2, 3].

Improvements in CT technology have led to significant progress toward achieving this goal. One method detailed elsewhere is the combination of CTA and CT perfusion (CTP) performed using adenosine stress. To date, the most comprehensive assessment of this methodology [4] assessed the combination of CTA plus CTP with respect to reference standard ICA plus single photon emission computed tomography (SPECT) [5]. CTP was shown to significantly enhance the accuracy of CTA alone, based on independent core laboratory reads from all 4 imaging modalities [2]. This study used only the morphology of the coronary arteries from the perspective of anatomical evaluation of coronary stenosis.

Newer generation CT hardware has provided improved spatial and temporal resolution and larger volume coverage [6, 7]. Specifically, the larger volume coverage enables the

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extraction of flow-dependent information from contrast enhancement patterns in first pass CTA images. In this way, current technologies are capable of characterizing the attenuation of contrast medium in coronary arteries [8], and these data can in turn be used to evaluate both the degree and direction of contrast flow, as it is carried along by the blood [9, 10].

Based on this concept, there is a new family of parameters that have been developed to quantify the contrast density variations in routine coronary CTA DICOM images [11]. All of these parameters are based upon 1 of the author's (F.R.) clinical observation and clinical follow-up regarding patients who have CT lesions that ultimately undergo an intervention for CAD at Brigham and Women's Hospital in Boston, MA, USA. The observation is that CT attenuation as measured in Hounsfield unit (HU) differs from the proximal to the distal coronary artery, and those coronary arteries that are associated with events in follow-up have a greater HU drop off from proximal to distal artery than those vessels that are not associated with events. Although this observation is simple and clinically reliable for a technically adequate scan, the physics of blood flow are very complex, and there are many potential methods to determine those scans that should be considered adequate. For cardiovascular imagers who acquire and interpret coronary CTA images for patient management decisions, there has been a discussion regarding the ability to see substantial HU drop offs with the naked eye vs making region-of-interest (ROI) measurements. It is 1 of the author's (F.R.) opinion that many coronary CTA interpretations are performed with too much ambient room lighting, and simply adjusting the reading room to one tailored for clinical interpretation of images can make several aspects of the interpretation more favorable. Moreover, there are now multiple software packages that will compute these parameters along with the coronary vessel segmentation. When used, these software package results should be correlated with the appearance of the images, similar to using software that automatically judges the degree of stenosis from an individual coronary lesion.

This article reviews and interprets the several publications that test this family of new coronary CTA parameters for the hemodynamic significance of coronary stenosis. There are 2 basic parameters, and both are based on HU measurements (ie, ROI measurements), in the coronary lumen. The first parameter reflects the difference between 2 points in the coronary artery such as the proximal and distal left anterior descending (LAD). Another way to place the 2 points more closely would be just proximal and just distal to a coronary lesion. This measurement is called a contrast opacification difference, or for simplicity a "contrast difference." For the second parameter, many, as opposed to 2, points are placed within a coronary artery. These points then map the opacification pattern along the vessel. The contrast opacification can then be plotted with respect to a standard denominator such as the distance along the coronary artery. This is termed the contrast opacification gradient for the coronary distance, and it is defined as the linear regression coefficient of the HU vs distance from the coronary ostium (Fig. 1). There is no theoretical difference between the contrast opacification gradient with respect to distance and the transluminal attenuation gradient, or "TAG", except for the fact that the concept was hypothesized, tested, and published [12••] using initial CT images acquired from 320-detector row CT hardware. The "TAG" was later applied first to 64-detector row CT acquisitions, and this abbreviation was subsequently applied to 320 CT acquisitions. As noted below, the sampling rate along the coronary artery has varied in the reported data. In summary, we recommend that all these data together be termed "contrast gradients" or "gradients" to reflect the distinction from contrast differences.

In addition to the definition and historical description above, the purpose of this article is to instill among cardiac imagers the fact that CT contrast enhancement in the coronary lumen provides more information than the simple separation of the lumen and the surrounding structures. Simply put, the data in the contrast opacification is related to blood flow, for it is that flow that delivered the contrast at the point in time when the CT data was acquired. The text below is intended to illustrate these techniques, summarize the results to date, and review limitations that require future studies. It is likely that in the near future such novel yet simple approaches to quantify the flow of contrast will allow enhanced prediction of functionally significant stenoses from coronary CTA by enhancing specificity, particularly in cases where evaluation is otherwise difficult [13, 14, 15•, 16].

Contrast Opacification in Coronary CT Images

The initial evaluation of 320-detector row coronary CTA reported consistently lower contrast density in distal normal coronary arteries compared with proximal arteries [8]. Further analysis of this phenomenon led to the discovery of the contrast gradient, namely, that this drop-off in contrast enhancement along the length of a coronary artery is both continuous and highly linear, as well as smaller in normal coronaries than in those with significant diameter stenosis ≥75 % [12••].

The physical principles describing the time-varying concentration of a contrast bolus injection at the entry and exit of a circulatory subsystem, under the assumption of no recirculation, were described in the mid-1950s and early 1960s [17, 18]. These basic principles can be applied to the first pass iodinated contrast passage in all CTA data (including the coronary arteries) because the HU of blood linearly relates to the concentration of the contrast agent [19]. Based on this theory, both brain [20] and myocardial [21] flow have been measured by CT, although widespread clinical use is limited by technical and radiation dose considerations because accurate data requires continuous imaging throughout the bolus passage. Nonetheless, because the proximal and distal segments of a single artery without any intervening bifurcations

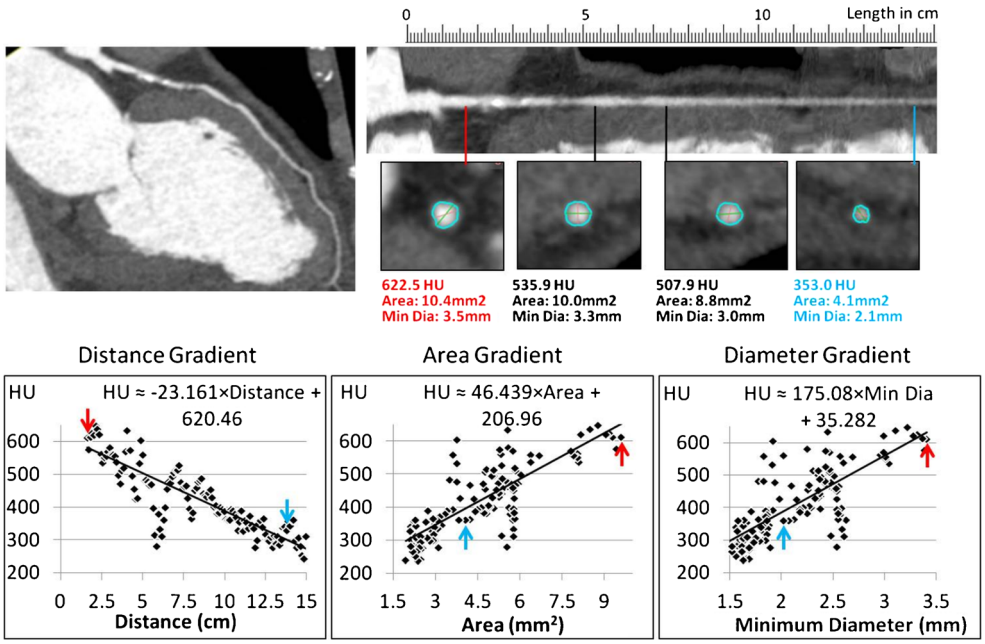

Fig. 1 Illustration of contrast opacification gradients. The top left image illustrates the course of the LAD with respect to the myocardium. The straightened reformatted image with corresponding ROI HU measurements appears on the top right. The lower panels show the regression lines that define the gradients. The distance gradient (*bottom left*) is most commonly reported. *HU* Hounsfield unit, *LAD* left anterior descending, *ROI* region-of-interest

also form a subsystem with a single entry and exit, contrast bolus passage curves at any 2 such arterial locations can similarly be used to quantify blood flow. The discovery of the contrast gradient in normal and obstructed coronary arteries using CTA [12••] first suggested that CT is sufficiently sensitive to detect contrast concentration differences that reflect the time delay in the contrast bolus passage between 2 coronary arterial locations.

Our initial findings were further validated in vitro by Lackner et al. who thoroughly analyzed the temporal patterns of CT attenuation in conduits with caliber similar to coronary arteries, and with varying stenosis severities [9]. Coronary arteries were simulated using 3 mm inner-diameter silicon tubes with 15 mm-long stenoses between 50 % and 90 % diameter reduction. Dynamic imaging of these phantoms was performed using both 16- and 64-detector row CT during the injection of contrast in saline pumped with a pulsatile flow profile. For 16-detector CT at a temporal resolution of 210 ms, stenoses ≥70 %, 80 %, and 90 % could be excluded with 99 % confidence using cut-offs for the slope of peak density increase vs time. With 64-detector row CT at 270 ms temporal resolution, cut-off values of the slopes could exclude stenosis ≥80 % or 90 %, but stenosis ≥70 % could not be confidently excluded [9]. The results of this study validated that current CT technology can detect the level of variations in contrast concentration that are induced by blood flow.

Contrast Opacification Gradients

The introduction of gradients evaluated both normal coronary arteries and LAD arteries with stenosis using 320-detector row CT. The gradient values were computed from 1-mm equidistant intervals along the vessel using automated post-processing software [12••]. The "distance gradient" was described as a linear regression between intraluminal contrast opacification (mean HU) and distance from the ostium. In addition to distance gradient, lumen cross-sectional area (Ga) and lumen short axis diameter (Gs) gradients were assessed (Fig. 1); all 3 metrics revealed high reproducibility with insignificant variations between cardiac phases, heart rates, body mass index, and between readers. This study reported the linear relationship of HU reduction against vessel distance, with higher rate of HU reduction with significant artery stenosis. The Ga and Gs assessments revealed significant non-zero slope or gradient ($P<.0001$), with excellent or good goodness-of-fit in all 3 gradients and no difference between the 3 coronary arteries for Ga and Gs. The comparison of the gradients revealed a significant mean value difference between patients with or without significant stenosis ($P=.021$), with Gs providing the most consistent difference in the mean value [12••]. For assessment of distance gradient across a single lesion in a coronary artery, differences in the attenuation values across the lesion was divided by the length of the lesion and studies have proven larger gradients to exist across lesions compared with normal coronary arteries.

One way to measure the gradient is to make intraluminal ROI measurements of the average attenuation in cross-sections of the artery orthogonal to the centerline at fixed intervals along its course, starting at the coronary ostium and extending to the distal artery. These manual tracings can be performed at a 5–10 mm interval, which has been assumed sufficient. Using semi-automated software, tighter spacing of 0.5–1 mm intervals have been used to obtain more data points

[8, 11, 12••, 13, 15•, 16, 22]. Another variable is the most distal spot in the coronary artery to make the HU measurement. To date, this has been chosen using a diameter cutoff of 2– 2.5 mm or an area cutoff of 2 mm^2 [8, 11, 12••, 13, 14, 15•, 16, 22]. Similarly, the ROI used to perform the intraluminal contrast attenuation measurement has been operator-dependent, and has been either the entire luminal contour, or a small ROI of fixed 2 mm^2 area placed manually within the lumen.

As noted above, when the number of HU measurement is reduced to 2, a proximal and distal point along a coronary artery, the gradient is subsequently reduced to an opacification difference. Although the difference alone does not include distance traveled by contrast between measurement sites, 1 of the requirements to calculate flow velocity, its usefulness has been established for coronary artery lesions [13, 22, 23]. The first comparison of contrast opacification changes in a vessel with respect to ICA was performed by Chow et al. who developed and compared opacification differences against both anatomic severity by ICA and functional severity in terms of blood flow as defined by the thrombolysis in myocardial infarction (TIMI) grade in 52 patients [23]. This study used 64-detector row subvolume CT, and because there is temporal nonuniformity in the coronary arteries, the proximal and distal coronary HU values were normalized by dividing the coronary ROI mean HU by the attenuation in the aorta on the same axial slice. The contrast difference in normal arteries was found to be 0.100±0.042. The difference was significantly different than that found both in arteries with obstructive CAD as defined by ICA (≥50 % diameter stenosis; difference=0.191±0.214), as well as in arteries with TIMI flow grade <3 (difference=0.406±0.226), although it was not changed (difference=0.078±0.078) compared with arteries with TIMI flow grade of 3 [23]. That is, while the opacification difference was not changed from normal for arteries with nonflow obstructive lesions, it was somewhat higher than normal for anatomically obstructive lesions (P=.004) and much higher (P<.001) for vessels with abnormal resting coronary flow [23].

Based on a thorough analysis of the variability of the opacification difference in normal arteries, a cut-off for the difference of >0.184 was used to detect abnormal coronary flow (TIMI flow grade <3) with an overall accuracy of 89 % [23]. In addition, when comparing vessels with stenoses ≥50 % against normal vessels, the minimum normalized contrast opacification found proximal to a stenosis was slightly higher than normal vessels (P=.006), while the minimum normalized contrast opacification poststenosis was significantly lower (P<.001). This finding correlated to decreased contrast flow through the stenotic lesion, resulting in more contrast medium accumulation in the prestenosis region compared with poststenosis segments. The study noted that measurement of the opacification difference may be particularly beneficial in arteries otherwise difficult to evaluate, such as those with severe coronary calcification or stents [23]. It additionally stressed the importance of correcting for the temporal variation in coronary contrast opacification at different heart beats as occurs with 64-detector CT, using the opacification in the descending aorta acting as the normalizing factor because assessment of CAD severity was not possible by contrast opacification measurements without this correction [23].

Choi et al. first assessed gradients for the detection of significant stenosis in comparison to both ICA and TIMI flow measurements in 126 patients [13]. Although they used 64-detecor row hardware, there was no correction to account for the subvolume imaging. Nonetheless, their results mirrored those from our group [12••], namely that the gradient became more abnormal according to increasing stenosis severity by CT, as well as in accordance with quartiles of segmental stenosis and segment-at-risk scores. A consistent and significantly lower gradient value with increasing maximum stenosis severity on a per artery basis was also observed against invasive assessment by quantitative ICA, with gradient values ranging from –2.37±–4.67 HU/10 mm for lesions with less than 50 % stenosis to –13.46±–9.59 HU/10 mm for diameter stenosis of 100 % (P<.0001) [13]. Importantly, in keeping with our study [12••], gradient values were different among the 3 coronary territories, with marked differences between left and right coronaries. For example, among LAD and left circumflex (LCX) arteries with <50 % stenosis by ICA, gradient values were –2.93±5.14 and –3.62±5.16 HU/10 mm respectively, while in right coronary arteries (RCA) with <50 % stenosis, they were –0.16±2.08 HU/10 mm. This difference persisted across stenosis severity levels; for example in 70 %–99 % stenosis, the values for the LAD, LCX, and RCA were –11.6±5.91, –13.99±9.18 and –9.24±6.3 HU/10 mm, respectively.

In terms of invasively measured resting flow, these results mirrored those of Chow et al. [23], with gradients correlating to both TIMI grade as well as corrected TIMI frame count. In addition, in arteries with 100 % stenosis or TIMI grade 0, the gradient correlated (P<.0001 for all comparisons) to Rentrop grade classification of collateral flow [13]. Finally, the addition of the gradient to the CT based stenosis classification significantly enhanced accuracy compared with CT alone for the detection of obstructive CAD ≥50 % stenosis by ICA [area under the curve (AUC) of the receiver operating characteristic (ROC) curve 0.951 vs 0.932]. This was also true for either calcified or noncalcified plaques independently (ROC AUCs of 0.880 vs 0.825 and 0.978 vs 0.960, respectively). However, results were less encouraging for the reclassification of patients, with the net reclassification improvement index compared with CT alone becoming significant for only calcified (>30 % calcification by volume) plaques [13].

Contrast Opacification Gradients and the Hemodynamically Significant Coronary Lesion

The first study of the physiological significance of gradients and opacification differences was also performed by Choi et al. in 97 arteries with luminal diameter stenosis ≥50 %, and invasive FFR less than or equal to 0.8 as the reference standard for myocardial ischemia [22]. Forty-one percent of vessels had a lesion with significant FFR. For the prediction of significant FFR, gradients had low sensitivity (47.5 %) but high specificity (91.2 %), in contrast to CT that had high sensitivity (92.5 %) but low specificity (52.6 %). The contrast differences alone had moderate sensitivity and specificity (65 and 61.4 %, respectively). The addition of gradients to the CTA read of morphology alone significantly increased the ROC AUC (0.809±0.044 vs 0.726±0.056), but addition of the opacification differences to CT did not (AUC 0.784± 0.048). However, addition of the gradients to the CT did not lead to significant improvement in the net reclassification index, while addition of differences to the CT reads led to its impairment [22]. The main explanation noted in these results was that both contrast metrics were obtained from a rest coronary CTA, while FFR is assessed under pharmacologically-induced stress [11, 22]. Rest flow does not adequately correlate to coronary hemodynamics for a lesion with <85 % stenosis [24].

A second study of 64-detector row coronary CTA to predict invasive FFR was published by Yoon et al. [16]. This study focused on the comparison of the diagnostic value of gradients and coronary CTA-derived FFR. This is typically denoted FFR_{CT}, and results are detailed [25–27] in other articles. Among 82 vessels, 39 % of which had lesions with FFR≤ 0.8 [16], both the gradient and FFR_{CT} were significantly lower in vessels with lesion-specific ischemia than in those without. The ROC AUC of the gradient alone was 0.63 (gradient sensitivity and specificity of 37.5 % and 88 %, respectively) and not significantly different than that of coronary CTA, whereas that of FFR_{CT} was 0.94 (sensitivity and specificity of 81.3 % and 94 %, respectively), significantly higher than that of coronary CTA. However, in the subset of calcified lesions, none of the 3 tests had significantly different AUCs. Interestingly, the gradient results in this study were equivalent to those found by Choi et al., including sensitivity, specificity and AUC measures. Unfortunately, however, this study opted for a "head-to-head" comparison of FFR_{CT} against gradients as stand-alone diagnostic tests, rather than using the combined test of gradients plus coronary CTA, for which prior studies had established that the high specificity of the gradients could be combined with the high sensitivity of CT.

Wong et al. first evaluated the diagnostic accuracy of gradients and differences using single heart beat 320-detector row coronary CTA images against invasive FFR in 78 vessels [16 •]. These images have temporal uniformity because the 16 cm craniocaudal field of view covers the entire heart [28]. Of note, at the time of writing, gradients have not been analyzed using high-pitch dual source CT; such acquisitions occur at different time points in diastole over a single R-R interval [29]. In the Wong et al. study, the gradients were significantly lower in vessels with lesions with FFR ≤0.8 than in those with FFR >0.8 (median –21 vs –11 HU/10 mm). A gradient cutoff value of –15.1 HU/10 mm had sensitivity and specificity to detect functionally significant ischemia of 77 % and 74 %, and positive predictive value and negative predictive value of 67 % and 83 %, respectively. The gradient provided incremental predictive value to CT, significantly increasing the ROC AUC (0.89 for TAG plus coronary CTA, vs 0.814 for the gradient alone, vs 0.79 for coronary CTA alone), and with evidence that incorporation of the gradient enhances both the sensitivity and specificity of coronary CTA to detect lesion-specific ischemia [15•]. Finally, no difference in diagnostic accuracy was found based on plaque composition. All contrast opacification differences were significantly higher in arteries with FFR ≤0.8 compared with arteries with no functionally significant lesions. However, the opacification difference was not independently predictive of FFR ≤0.8 when the CT reads alone plus the gradients were already included in the multivariate model, and no further analysis of the difference was warranted because overall accuracy of using the gradient (ie, more data points) was higher than the HU difference between the proximal and distal coronary artery [15•].

Another contrast enhancement pattern that can be used clinically has been termed the reverse attenuation gradient sign, or a "reverse gradient." This term was coined by Li et al. [30], although Choi et al. noted in the literature that gradients correlate with Rentrop collateralization grade [13]. The reverse gradient is very common and also can be seen with the naked eye; it refers to a drop off in attenuation from proximal to distal along a coronary artery, after which there is a paradoxical increase in attenuation. In coronary CT image interpretation, there is typically a sharp drop in HU followed by a dramatic rise in enhancement. The reason is collateral flow. Accordingly, Li et al. described the published the finding as a highly specific predictor of chronic total coronary occlusion [30]. Chronic total occlusion is reported to be found in more than 20 % of patients with suspected coronary artery disease and as many as one-third of patients with at least 1 vessel with >50 % stenosis at ICA [31–34]. At our institution, cardiac CT has been used for a decade to identify the features that render candidates suitable for successful intervention [35], and aid the operator in percutaneous procedure planning [31]. Incidentally, 1 of the authors (F.R.) has used the same finding in the abdomen to determine total vs subtotal occlusion in the mesentery, were collateral flow in patients with an occluded celiac axis or superior mesenteric artery is very common.

Mathematically, patients with a reverse gradient have a positive (increasing) HU trend in segments distal to the lesion in question. In distinction, patients with a subtotal occlusion, for example a high-grade stenosis with retained antegrade flow, maintain a negative (decreasing) HU trend distal to the stenosis. It is reported that when the reverse gradient sign is absent, there may be some collateral flow, and similarly, bridging collaterals can still lead to the absence of the reverse gradient sign in patients with chronic total occlusion. Nonetheless, in a series of 94 occlusive lesions, Li et al. demonstrated a gradient of 5.1 HU/10 mm±13.4 for lesions with chronic total occlusion vs –13.4 HU/10 mm±8.7 for subtotal lesions. These data were acquired using single source 128-detector row scanner. The reverse gradient was present in 65 % of chronic occlusions and 7 % of high-grade but patent lesions.

Conclusions

Before the advent of hardware and techniques that allowed the analysis of first pass CTA contrast opacification within the course of the coronary arteries, iodine enhancement was used only to identify the vessel lumen and differentiate it from the wall and intervening lesions. In our opinion, and supported by the data reviewed in this article, this represents an underutilization of CTA data in general, and specifically an underutilization of coronary CTA where flow-dependent information can be critical for patient management. The second take-home message is that contrast differences and gradients (ie, the metrics themselves) are no more than a mathematical representation of what one can observe when reading a coronary CTA study. The fluid mechanics of the flow and how it is imperfectly captured by a CT scanner are orders of magnitude more complex, despite the fact that the clinical observation is simple. This is the reason why gradients may not "work" as cleanly as one might expect if a simple equation is applied to a coronary lesion. However, there are large amounts of visual data in the enhancement patterns, and these data should be considered in image interpretation. Finally, we believe that contrast differences and gradients have the favorable quality of being simple to understand and simple to see and compute. Thus, visual assessment and quantitative information can be easily incorporated into cardiac imaging workflow.

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Compliance with Ethics Guidelines

Conflict of Interest Frank J. Rybicki receives research support from Toshiba Medical Systems Corporation. Yu-Hsiang Juan, Sachin S. Saboo, Elizabeth George, Rani Bhivasankar, and Dimitrios Mitsouras declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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