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Introduction and Outline

Clinical Application of CT Coronary Angiography: State of the Art

FR de Graaf, JD Schuijf, V Delgado, JE van Velzen, LJ Kroft, A de Roos, JW Jukema, EE van der Wall, JJ Bax

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ABSTRACT

In recent years, multidetector computed tomography (CTA) technology has developed rapidly, allowing high-resolution non-invasive imaging of the coronary arteries and surrounding structures. Since the introduction of CTA, acquisition time, detector number, spatial and temporal resolution have continuously improved with each new scanner generation, resulting in excellent image quality and diagnostic accuracy in the detection of coronary artery disease (CAD). At the same time, developments in CTA technology have focused on reduction of the radiation dose. In particular, the availability of dose modulation and prospective ECG gating have drastically reduced patient radiation dose. Moreover, with the introduction of 320-row CTA, volumetric scanning of the entire heart has become possible in a single heart beat or gantry rotation, thereby eliminating oversampling and stair-step artifact. The present article provides an overview of state of the art clinical applications of cardiac CTA, including the diagnosis of CAD, evaluation of plaque morphology and composition, prognostification, and the evaluation of left ventricular function and aortic and mitral valve anatomy.

INTRODUCTION

Over the past decade, multidetector computed tomography (CTA) technology has developed rapidly, allowing high-resolution non-invasive imaging of the coronary arteries and surrounding structures. Since the introduction of CTA in the early 1990's, acquisition time, detector number, spatial and temporal resolution have continuously improved with each new generation of scanners, resulting in excellent image quality and diagnostic accuracy in the detection of coronary artery disease (CAD).[1] Previous 4-, 16- and 64-row CTA systems used a helical scanning technique with retrospective ECG gating. Subsequently, dual-source CT was introduced with superior temporal resolution (83 ms) and excellent image quality, also at increased heart rates.[2] Simultaneously, developments in CTA technology have focused on reduction of the radiation dose. In particular, the availability of dose modulation and prospective ECG gating have drastically reduced patient radiation dose.[3 4] Finally, increased coverage has been achieved with the introduction of 320-row CTA. These systems allow volumetric data acquisition of the entire heart within a single gantry rotation, thereby eliminating oversampling and stair-step artifacts.[5 6] This novel system, in combination with prospective ECG modulation, represents another step forward in CTA technology. The present article provides an overview of state of the art clinical applications of cardiac CTA, including the diagnosis of coronary artery disease, evaluation of plaque morphology and composition, prognostification of patients with CAD, and the evaluation of left ventricular function and aortic and mitral valve anatomy.

DIAGNOSIS OF CORONARY ARTERY DISEASE

Evaluation of Patients with Suspected CAD

Cardiac imaging is complicated by the rapid, nonlinear movement of coronary arteries. Previously, direct visualization of the coronary arteries was limited to invasive techniques, such as coronary angiography. However, with the introduction of CTA non-invasive evaluation of CAD has become possible (figure 1 and 2). Although temporal and spatial resolution of CTA remain inferior as compared to conventional coronary angiography, high diagnostic accuracies have been demonstrated for the detection of significant CAD.[7]

Multiple studies have shown good sensitivity and specificity of 64-row CTA, currently the most widely used system, for the detection of obstructive lesions as compared to conventional coronary angiography.[8 9] In a recently published multi-center trial, diagnostic performance of 64-row CTA was investigated in 291 symptomatic patients with suspected CAD. On a patient basis, sensitivity and specificity were 85% and 90%, respectively.[9] Moreover, a recent meta-analysis by Mowatt et al, evaluating 28 studies using

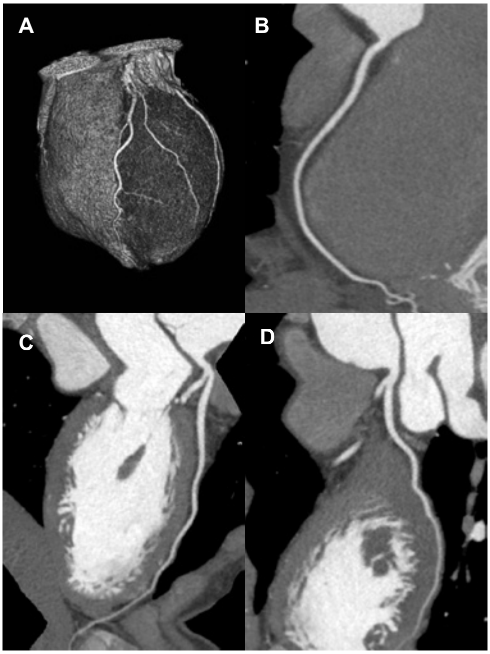

Figure 1. Normal CTA coronary angiogram. A 60 year old diabetic female with atypical chest pain underwent 320-row CTA coronary angiography. CTA showed normal coronary arteries, and the patient was discharged. Three-dimentional reconstruction of the heart (A). Curved multiplanar reconstructions of the RCA (B), LAD (C) and LCx arteries (D) revealed the absence of atherosclerotic abnormalities.

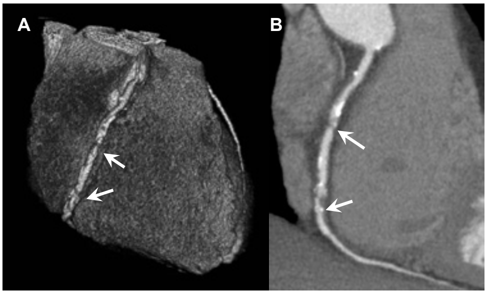

Figure 2. CTA coronary angiogram with obstructive atherosclerosis. A 68 year old smoker presented with suspected ACS to the emergency department. Biomarkers remained negative while evident ECG changes were also absent. The patient was referred for 320-row CTA to evaluate the presence of CAD. Three-dimensional volume rendered reconstruction showed multiple stenoses in the RCA (arrows) (A). Also on the curved multiplanar reconstruction of the RCA multiple significant lesions can be observed, with both non-calcified and calcified components (arrows) (B).

64-row CTA in the assessment of CAD, reported pooled estimates of 90% sensitivity and 97% specificity on a segment-basis.[10] The negative predictive value across studies was 99%, demonstrating an excellent ability of CTA to exclude significant CAD. Furthermore, high diagnostic image quality has been reported for dual-source CT, without restrictions concerning heart rate. Alkadhi and colleagues recently reported sensitivity, specificity and positive and negative predictive values of 96.6%, 86.8%, 82.6%, and 97.5%, respectively.[11] Finally, the recent introduction of 320-row CTA has further reduced acquisition time and contrast administration and also eliminates stair-step artifacts seen in helical scanning techniques. Preliminary observations with this novel technique show promising results with respect to image quality and diagnostic performance.[5 6]

It is important to realize that the diagnostic performance of CTA coronary angiography may be influenced by the pretest likelihood of significant CAD, as demonstrated by Meijboom et al.[12] Due to its high negative predictive values, the main strength of CTA is its ability to rule out CAD. Accordingly, this technique may be particularly useful in the evaluation of patients with a low to intermediate pretest likelihood of having significant CAD. Patients with a normal scan may be discharged safely, whereas patients with significant atherosclerosis may be referred for functional imaging to aid further patient management.[13] Finally, when the pre-test likelihood of CAD is high, conventional coronary angiography remains the test of first choice and the additional value of non-invasive coronary angiography may be limited.

Of note, several limitations of CTA coronary angiography remain despite current developments. Importantly, the diagnostic accuracy of CTA is inversely related to vessel diameter while the presence of extensively calcified plaque may cause overestimation of stenosis severity.[14 15] Finally, the evaluation of degree of lumen stenosis is limited to visual assessment, while no validated quantitative algorithms are yet available for this purpose. To improve accuracy and reproducibility, a validated approach to stenosis quantification would be desirable.

Evaluation of In-stent Restenosis

Coronary stent implantation is routinely used in the treatment of patients with obstructive CAD. Nonetheless, after coronary intervention in-stent restenosis may occur, which requires early detection and fast treatment. Although visualization of stent lumen was difficult with early 4-row CTA systems.[16] reasonable stent-visualization became feasible with in 16-row CTA.[17] Nevertheless, also in these systems, evaluation of stent patency was hampered by blooming artifacts caused by the metallic stent strut.[18] Disturbances were particularly present in stents with high metallic content, thicker struts and small stent diameter.[19]

Using more advanced 64-row systems, in-stent lumen visibility increased significantly. Several studies reported good diagnostic accuracy in the evaluation of in-stent restenosis.[20 21] Cademartiri and coworkers reported a sensitivity and specificity of 95% and 93%, respectively, with only 7.3% of stents deemed uninterpretable.[21] In addition, a high negative predictive value (99%) was observed supporting the concept that CTA may be particularly useful in the exclusion of in-stent restenosis. Importantly, specificity in large diameter stents (≥3.0mm) was significantly higher than in small diameter stents (≤1.5mm). Similar findings were reported using dual-source CT by Pugliese and coworkers. The group demonstrated a sensitivity, specificity and negative predictive value of 94%, 92% and 98%, respectively.[22] However, also with this system, diagnostic accuracy was inversely related to stent diameter. Thus, in larger diameter stents, CTA may be a

Figure 3. CTA evaluation of stent patency. A patient with a history of recent anterior infarction and PCI was referred to CTA. Curved multiplanar reconstruction shows patency of the stent (diameter 3.5 mm) implanted in the LCx (arrow).

potential tool for the evaluation of stent patency and in-stent restenosis (figure 3). However, even with novel high-resolution systems, lumen visualization in small diameter stents remains limited.

EVALUATION OF PLAQUE MORPHOLOGY AND COMPOSITION

In the development of cardiovascular events such as acute coronary syndrome (ACS), diffuse atherosclerosis and plaque composition may be predictive of adverse cardiac events.[23] Therefore, assessment of atherosclerotic plaque composition and morphology, besides luminal narrowing, may be an important step in the identification of plaque instability. Previously, identification of potentially vulnerable plaque was only possible using invasive investigations, such as intravascular ultrasound (IVUS) and optical coherence tomography. However, by quantification of attenuation values, non-invasive visualization of plaque composition has become possible using CTA.[24]

Several studies using CTA have suggested that the evaluation of plaque composition may be of interest.[25 26] Pundziute et al compared plaque composition and distribution using 64-row CTA as compared to virtual histology IVUS (VH IVUS) in 50 patients.[25] In patients with stable CAD, the majority of lesions detected by CTA were calcified (61%). On the contrary, in patients with ACS, the majority of lesions were mixed (59%) or non-calcified (32%) and only a small portion calcified (9%). Another study by this group revealed that lesions deemed vulnerable on VH IVUS were frequently identified as mixed lesions on CTA.[26] Similar findings were reported by Motoyama and colleagues.[27] The investigators showed that low plaque density, spotty calcifications as well as positive vessel remodeling on CTA are associated with ACS.[27]

Although CTA can generally differentiate calcified plaque from mixed and non-calcified plaque, further sub-division between lipid-rich and stable fibrous lesions may be challenging. Overlap of CTA attenuation values exists between plaque types and, moreover, variable factors during image acquisition, such as patient body weight, may further influence attenuation values.[28] Furthermore, the aforementioned study by Pundziute et al demonstrated that small amounts of calcium were present on VH IVUS in lesions deemed completely non-calcified by CTA.[26] Similarly, calcified lesions on CTA contained a substantial proportion of non-calcified plaque on VH IVUS. Therefore, although CTA may potentially provide an estimate of relative plaque composition and morphology, at current this technique does not allow precise characterization of plaque morphology. Dedicated approaches to improve the evaluation of plaque composition are currently under investigation, which include dual-energy CTA, dedicated contrast agents and the use of automated quantification software for the detection and quantification of changes in plaque burden by CTA.[29,30] Furthermore, large prospective studies are needed to further substantiate the clinical value of plaque characterization with CTA.

PROGNOSIS OF CAD

Recently, several studies have addressed the prognostic value of CTA in patients with known or suspected CAD.[31,32] A survival analysis by Min and colleagues, using 16-row CTA in the evaluation of 1127 patients with chest pain, showed that CTA allows identification of patients at increased risk for all-cause mortality.[31] Several CTA variables were identified as independent predictors of mortality, including plaque severity, degree of CAD, plaque distribution, plaque localization and the presence of 3-vessel disease. Conversely, it was observed that, during a mean follow up of 15 months, a normal CTA scan predicts a very low mortality risk (0.3%). Similar findings were reported in another recent study, using both 16-row and 64-row CTA.[32] Importantly, long-term follow-up results (average 6.5 years) were recently reported by Ostrum et al, who investigated 2538 symptomatic patients with electron beam tomography (EBCT) coronary angiography. The investigators showed that all-cause mortality risk was closely related to the extent of CAD as determined on EBCT and that this information was incremental to coronary calcium scoring.[33] Thus, it appears that CTA may be a valuable tool in the identification of patients at risk for adverse cardiac events. Patients with normal scans may be reassured, without the need for additional testing. Alternatively, patients with evident CAD on CTA, who are at increased risk for future cardiac events, may be referred for additional evaluation or medical treatment.

Furthermore, the anatomical information that is obtained by CTA may have additional prognostic value over functional testing. Indeed, a recent study by van Werkhoven et al, evaluating 541 patients, demonstrated that CTA variables were able to refine risk stratification with SPECT myocardial perfusion imaging.[34] Interestingly, plaque composition on CTA and the presence of non-calcified plaque in particular, was also predictive of adverse cardiac events. Therefore, in the evaluation of patients with CAD, CTA may not only provide independent prognostic information over baseline clinical risk factors but also over functional imaging. Additional research in large patient populations with increased follow-up is warranted to further substantiate the prognostic value of CTA.

EVALUATION OF CARDIAC STRUCTURES AND LEFT VENTRICULAR FUNCTION

Although the main application of CTA is non-invasive coronary angiography, the technique is not restricted to imaging of the coronary arteries alone. Using CTA retrospective reconstructions of cardiac images in any tomographic plane throughout the R-R interval may be obtained. As a result, high-resolution imaging of cardiac structures as well as the assessment of left ventricular (LV) function is possible. Accordingly, the clinical applicability of this technique is rapidly increasing beyond the noninvasive evaluation of CAD.

LV function

Evaluation of left ventricular function is an essential part of the management of patients with known or suspected CAD. Although echocardiography is the technique of choice, CTA may also serve as an accurate imaging modality for the non-invasive evaluation of global and regional LV volumes and function. LV measurements are of particular value for diagnosis, prognosis and therapeutic management.[35]

For the purpose of global LV function quantification, 10 or 20 sequential image data sets (each 2 mm thick) are typically reconstructed in the short-axis orientation at each 5 or 10% of the R-R interval. By means of selecting the smallest and largest cross-sectional LV cavity areas, end-systolic and –diastolic phases are determined. Subsequently, specialized semi-manual or automatic software is used to define the endocardial border of the appropriate phases, and using the Simpson method, end-diastolic and –systolic volumes are derived. Alternatively, after manually or automatically defining the LV axis and upper ventricular border, recently introduced algorithms may be used for volumetric measurements of the selected phases.

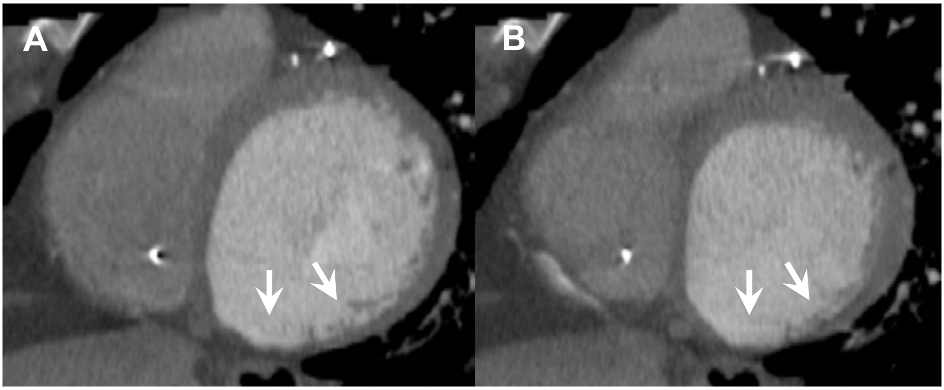

Figure 4. Evaluation of LV function with CTA. Short-axis view of end-diastolic phase (A) and end-systolic phase (B). Akinesia and thinning of myocardium can be observed in the inferolateral wall, due to previous myocardial infarction. Assessment of global LV function revealed a severely reduced LVEF of 18%.

CTA has previously been demonstrated as a feasible imaging modality for LV function assessment. In a study conducted by Henneman et al a good agreement was demonstrated for the assessment of LV ejection fraction in 40 patients when comparing 64-row CTA to 2D-echocardiography ($r=0.91$, $p < 0.001$).[36] Moreover, excellent correlations were demonstrated in the evaluation LV volumes and ejection fraction between CTA and Magnetic Resonance Imaging (MRI), the gold standard for non-invasive LV function assessment.[37] Importantly, LV volume measurements with CTA may even be more accurate than measurements with 2D-echocardiography. Indeed, a recent study by Yamamuro and coworkers showed that measurements between CTA and MRI were more closely related than measurements between 2D-echocardiography and MRI.[38]

In addition to global LV function assessment, regional wall motion may be assessed with CTA by displaying images in cine-loop format. For this purpose, a 17-segment model is used[39] and each segment is classified as normokinetic, hypokinetic or akinetic/dyskinetic (figure 4). Mahnken et al studied the feasibility of regional wall motion assessment using 16-row CTA in comparison to MRI. A good agreement was observed between the two modalities, with 86% of segments scored identically ($k=0.79$).[40] A more recent study on regional wall motion, using 64-row CTA, showed similar results.[41]

Novel acquisition protocols to reduce radiation exposure however do no longer offer the possibility to retrospectively acquire LV function measurements. Indeed, with the recent introduction of prospective ECG triggering, data are acquired during only a small portion of the cardiac cycle. As a result, these protocols decrease radiation dose, but also eliminate the possibility for simultaneous evaluation of cardiac volumes. Importantly, LV function may still be reliably evaluated, by combining prospective ECG triggering with ECG pulsing or dose modulation, however at the cost of increased radiation dose.

Aortic and mitral valve anatomy

Similar to the assessment of LV function, echocardiography remains the technique of choice for the evaluation of patients with valvular heart disease, and CTA has no evident role in the initial assessment of these patients. Nevertheless, CTA may be of value in the detailed evaluation of valvular function, anatomy and morphology prior to percutaneous valve repair or replacement (PVR).[42 43] PVR techniques have been proposed as an alternative to surgical annuloplasty for patients who are unable to undergo surgery due to increased risk of peri-operative complications, such as elderly age or comorbidity.[44] To evaluate aortic and mitral valve anatomy and function, 10 sequential cine-loops are typically reconstructed in steps of 10% throughout the cardiac cycle, using ECG gating. Subsequently, visualization of leaflet or cusp motion is obtained by displaying these reconstructions in cine-loop format.

For the purpose of coronary sinus annuloplasty, a percutaneous approach for mitral valve repair, precise knowledge of the anatomical relationship between the mitral annulus and the coronary sinus is essential. To determine the best treatment strategy, CTA images in a plane perpendicular to the valve are typically used to demonstrate mitral valve anatomy and surrounding tissues. Importantly, the feasibility of the intervention depends on the distance between the coronary sinus and the mitral annulus in addition to the anatomical relationship of these two structures with respect to the course of the left circumflex coronary artery (LCx). Previously, Choure et al, using 16- or 40-row CTA for the evaluation of patients with mitral valve prolaps, demonstrated that the distance between the coronary sinus and mitral annulus increased proportionally in patients with mitral annular dilatation.[45] Moreover, the LCx crossed between the coronary sinus and mitral annulus in the majority of patients (80%), posing a risk for impingement and subsequent infarction. Similar results were found by Tops et al, using 64-row CTA.[46] Thus, initial results demonstrate that CTA may be a valuable imaging modality in the selection of potential candidates for percutaneous mitral valve repair.

Percutaneous aortic valve replacement has been introduced as an alternative to surgical treatment in patients with severe symptomatic aortic stenosis.[47-49] Similar to percutaneous mitral valve repair, careful pre-procedural screening may prevent complications, such as the presence of para-valvular aortic regurgitation or occlusion of the coronary ostia. Important pre-interventional measurements include aortic annulus sizing, evaluation of the aortic root and surrounding tissues, including the coronary ostia, amount of calcification and morphology of the aortic valves (figure 5). With CTA, optimal aortic

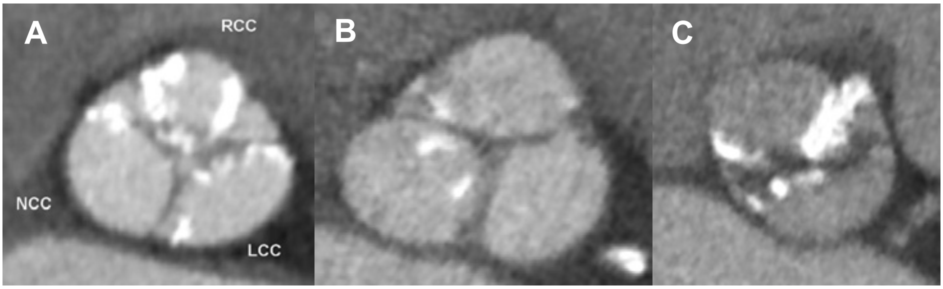

Figure 5. CTA assessment of aortic valve anatomy and morphology. Variations in morphology and anatomy can be identified using CTA. Heavily calcified tricuspid valve (A). Tricuspid valve with minor calcifications (B). Heavily calcified bicuspid valve (C).

valve visualization is obtained by reconstructing images in a cross-sectional plane perpendicular to the valve cusps. In a study by Tops et al, a detailed assessment of the aortic root anatomy was performed using 64-row CTA.[50] The study revealed an oval shape of the aortic annulus (diameter 26.7 ± 3.9 mm on the coronal view, 24.5 ± 3.0 mm on the sagittal view) in a sub-population of patients with aortic stenosis. Moreover, in nearly half of all patients, the length of the left coronary leaflet was larger than the distance between the annulus and the left coronary ostium. Therefore, detailed non-invasive evaluation of the aortic root with CTA may guide intervention strategies and may be important in avoiding coronary ostium occlusion by bulky leaflet after device positioning and para-valvular leakage. Thus, CTA may facilitate the pre-interventional selection of potential candidates and optimal treatment strategies for PVR. However, prospective studies in larger cohorts are needed to support the use of CTA in the setting of PVR patient selection and to evaluate the benefit of this technique on procedural outcome.

Myocardial Perfusion Imaging

An important limitation of CTA is the fact that it cannot provide information on the hemodynamic consequences of a detected lesion. Comparative studies between CTA and functional imaging techniques have revealed a substantial discrepancy between the presence of a stenosis on CTA and the presence of ischemia on functional testing.[51] Since the presence and extent of ischemia is important in determining further management, additional testing is frequently required in case of an abnormal CTA scan.

To overcome this limitation, the feasibility of CTA myocardial perfusion imaging in combination with CTA coronary angiography is being investigated. Using changes in myocardial tissue attenuation during CTA contrast administration, perfusion defects may be identified during stress and rest imaging. To this end, several approaches are available, depending on the CTA system used. Explorative studies have described a dynamic imaging approach for absolute quantification of myocardial perfusion, in which attenuation differences are dynamically detected over time during the entire infusion of contrast media.[52] A major drawback of this protocol is that it requires prolonged acquisition time and increased radiation exposure. Moreover, dynamic imaging using 64-row CTA is only able to scan a selected portion of the heart, rather than the entire heart, which limits its clinical application.

A second approach to CTA myocardial perfusion imaging is ECG gated helical scanning. This protocol is used by 64-row CTA systems and achieves full cardiac coverage by scanning the entire heart in multiple heartbeats. During image acquisition, retrospective ECG gating allows reconstructions of the entire heart during any phase of the cardiac cycle. Advantages of helical scanning technique are full cardiac coverage and reduced radiation exposure when compared to dynamic imaging. However, since data are acquired during several heartbeats, attenuation artifacts may occur. Furthermore, only semi-quantitative evaluation is possible with this approach.[53]

The recent introduction of 256- and 320-row CTA systems has enabled volumetric scanning, covering the entire heart within a single rotation.[5 6 54] Using a dynamic imaging approach, myocardial perfusion imaging of the entire heart may be performed in a single rotation, resulting in full cardiac coverage with homogenous attenuation of the myocardium. Preliminary data suggest that, with this approach, myocardial perfusion may be assessed either visually or semi-quantitatively.[55 56]

Thus far the majority of data concerning myocardial perfusion imaging has been obtained in animal models and only few observations in patients have been reported[57 58]. Recently, Kurata et al performed adenosine stress CTA myocardial perfusion imaging using 16-row CTA in a small cohort of 12 patients. Interestingly, the authors reported an agreement of 82% in the evaluation of myocardial perfusion defects when compared to SPECT.[58] Obviously, additional data are needed before CTA myocardial perfusion imaging can be applied in clinical practice.

CONCLUSION

CTA is a rapidly developing technique that allows non-invasive direct visualization of coronary anatomy. Importantly, due to its high negative predictive value, the technique may be particularly suited to rule out CAD. Similarly, after percutaneous coronary intervention, CTA may be valuable in determining stent patency as well as in-stent restenosis, although visualization of smaller stent lumina remains suboptimal. To some extent, CTA can provide information on plaque composition. Although exact identification of plaque composition and morphology remains difficult, the opportunity to directly visualize atherosclerotic plaques may offer an important advantage over invasive coronary angiography. Moreover, initial data suggest that this information can provide important prognostic information that is incremental over baseline clinical characteristics and other imaging techniques. Notably, the clinical applicability of cardiac CTA extends beyond noninvasive coronary angiography. Besides accurate evaluation of global and regional cardiac function, the detailed anatomical information on cardiac structures may also facilitate the selection of potential candidates for PVR. Finally, the potential to combine evaluation of coronary anatomy and myocardial perfusion in a single examination is currently under investigation, which could further optimize clinical assessment of patients with suspected or known CAD.

OUTLINE

The aim of this dissertation is to assess the role of advanced CTA for cardiac applications, in patients with known or suspected CAD. The dissertation constitutes two parts. **Part I** evaluates the diagnostic performance of 320-row CTA in the evaluation of patients with known or suspected CAD. The diagnostic accuracy of 320-row CTA in the noninvasive detection of significant stenosis (defined as ≥50% luminal narrowing) is assessed in **Chapter 2.** In **Chapter 3**, the diagnostic performance of non-invasive CTA is investigated in the detection of atherosclerosis (defined as) and significant stenosis. The value of CTA in the non-invasive evaluation of coronary stents and coronary artery bypass grafts is discussed in **Chapter 4**. Subsequently, the diagnostic performance of 320-row CTA to detect in-stent restenosis and the evaluation of coronary artery bypass grafts is described in **Chapters 5 and 6**. In **Chapter 7**, the diagnostic accuracy of 320-row CTA in patients presenting with chest pain is described. In **Chapters 8a and 8** the importance and efficacy of heart rate reduction prior to CTA beta blockade is explored. In **Chapter 9**, the effect of beat-to-beat motion of the coronary arteries on 320-row CTA image quality is discussed. The diagnostic performance of 320-row CTA in the evaluation of global left ventricular function is investigated in **Chapter 10**.
CTA has been suggested to be useful in patient risk stratification and as a gatekeeper prior to invasive coronary angiography. As a result, the purpose of **Part II** was to discuss clinical management in patients undergoing CTA. In **Chapter 11 and 12**, the potential role of CTA as a gatekeeper prior to invasive coronary angiography is discussed. The prognostic value of left ventricular function assessment over the assessment of significant stenosis on CTA is investigated in **Chapter 13**. Finally, the usefulness of the hypertriglycerdicemic waist phenotype to predict CAD on CTA in patients with type 2 diabetes is explored in **Chapter 14**.

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