Medical Radiology
Diagnostic Imaging

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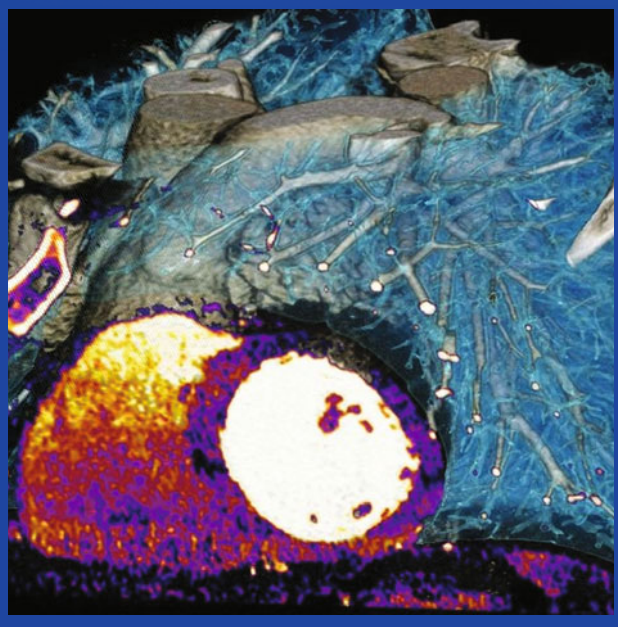
CT Imaging of Myocardial Perfusion and Viability

Beyond Structure and Function



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Preface

"...τὴν δὲ δὴ καρδίαν ἅμμα τῶν φλεβῶν καὶ πηγὴν τοῦ περιφερομένου κατὰ πάντα τὰ μέλι
σφοδρῶς αἵματος..."

Plato, Timaios, 360 BC

We are embarking on yet another exciting journey in our exploration of the determinants of the human body. Much has happened in the last decade that has decisively enhanced our abilities to noninvasively assess health and disease of the heart. Innovation in medicine ordinarily is a slow process; many years pass before a new test or procedure matures to the stage of universal acceptance and integration into clinical algorithms and guidelines. This process is welcome and necessary, as it ensures sufficient vetting of new techniques before they are applied on a large, universal scale and prevents unsuitable, unduly hyped fancies of the moment to enter the greater field of medicine. Because of its disruptive nature as the only noninvasive modality that enables interrogation of the coronary arteries, the use of cardiac CT has evolved at a breathtaking speed and has found entrance in general clinical practice, widespread acceptance, and inclusion into guidelines much faster than we could have dreamt of 15 years ago, when we embarked on applying modern era CT systems to cardiac imaging.

Now that general cardiac CT applications are firmly and irrevocably ensconced in the wider consciousness of medicine, it is time to explore new frontiers and further expand our boundaries. We are no longer content with mere morphe, it is the combination and interdependence of structure and function that tweaks our curiosity and ambition. In recent years, exciting new techniques have emerged that aim at the combined CT assessment of coronary artery disease and its consequences on the function of the heart muscle. These novel approaches have been enabled by constantly evolving technical innovation and by the ingenuity of clinicians and researchers who explore ever new avenues for applying our technical prowess to improving the human condition. The concomitant application of CT techniques for detecting coronary artery stenosis and their relationship to myocardial function, ischemia, infarction, and viability is of particular attractiveness. One single, rapid modality can comprehensively and noninvasively provide all information, whereas in past decades a barrage of multiple tests was required to obtain similar insights for the purpose of guiding beneficial and appropriate patient management. As such, CT imaging of myocardial ischemia, infarction, and viability is a true paradigm for the synergies that we need to create to face our challenges in the healthcare of the future.

We are proud to present to you the first tome on these exciting new developments in imaging and we hope that you will share our excitement. We are exceedingly grateful to our many expert contributors from around the globe who made time in their busy schedules to bring to you their cutting edge experiences in the application of a broad spectrum of approaches to tackle this fascinating feat. Our gratitude goes out to our dear friend Max Reiser for setting us on this path and to the editorial team at Springer who again so expertly steered the realization of this ambitious project.

Charleston, Munich, Toronto, Liverpool, Groningen, October 2013 The Editors

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Abbreviations

ABG	Coronary artery bypass grafting
ACS	Acute coronary syndrome
ACS	Acute coronary syndrome
AP	Angina pectoris
ATP	Adenosine triphosphate
CABG	Coronary artery bypass graft
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAD	Coronary artery disease
CAD	Coronary artery disease
CAD	Coronary artery disease
CAD	Coronary artery disease
CCA	Conventional coronary angiography
CCTA	Coronary computed tomography angiography
cCTA	Coronary computed tomography angiography
CCTA	Coronary CT angiography
cCTA	Coronary CT angiography
CHF	Congestive heart failure
CMR	Cardiac magnetic resonance
CT	Computed tomography
CT	Computed tomography
CTP	CT stress myocardial perfusion
CTP	Myocardial perfusion computed tomography
DECT	Dual-energy computed tomography
DECT	Dual-energy computer tomography
DSCT	Dual-source computed tomography
DSE	Dobutamine stress echocardiography
ECG	Electrocardiography
ED	End diastolic
ED	End-systole
EF	Ejection fraction
ES	End systolic
ES	End-systole
FDG	Fluorine-18-labeled deoxyglucose
FFR	Coronary fractional flow reserve
FFR	Fractional flow reserve
FFR	Fractional flow reserve
HU	Hounsfield Unit
ICA	Invasive coronary angiography
ICA	Invasive coronary angiography
ICA	Invasive coronary angiography
IVUS	Intravascular ultrasound
LA	Left atrium

LDA	Low-density area
LGE	Late Gadolinium enhancement
LV	Left ventricle
LV	Left ventricular
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MBF	Myocardial blood flow
MBF	Myocardial blood flow
MBF	Myocardial blood flow
MDCT	Multi-detector computed tomography
MDCT	Multidetector computed tomography
MDCT	Multidetector CT
MDCT	Multidetector CT
MDCT	Multidetector-row CT
MI	Myocardial infarction
MI	Myocardial infarction
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
MPS	Myocardial perfusion scintigraphy
MPS	Myocardial perfusion scintigraphy or SPECT
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRP	MRI stress myocardial perfusion
MRPI	Magnetic resonance myocardial perfusion imaging
MVO	Microvascular obstruction
NPV	Negative predictive value
NPV	Negative predictive value
NPV	Negative predictive value
PCI	Percutaneous coronary intervention
PCI	Percutaneous coronary intervention
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PET	Positron emission tomography
PPV	Positive predictive value
PPV	Positive predictive value
PPV	Positive predictive value
PTP	Pretest probability
RA	Right atrium
RV	Right ventricle
RVEF	Right ventricular ejection fraction
RVOT	Right ventricular outflow tract
SPECT	Single photon emission computed tomography
SPECT	Single photon emission computed tomography
SPECT	Single-photon emission computed tomography
Tc	Technetium
TCFA	Thin-cap fibroatheroma

Part I
Structure

Coronary CT Angiography: State of the Art

John W. Nance Jr.

Contents

Abstract

Technical advancements in computed tomography have provided the basis for safe, rapid, noninvasive detection of coronary artery disease with high diagnostic accuracy. While there are well-established limitations in the pure anatomic assessment of coronary atherosclerosis, there is a growing body of data demonstrating that coronary computed tomography angiography provides valuable prognostic information and may have outcome and cost benefits over traditional diagnostic testing in selected clinical scenarios. Appropriate utilization necessitates proper technique and patient selection. The exact clinical role of computed tomography-based anatomic assessment of coronary artery disease is still evolving, and emerging techniques are encouraging for improved performance and expanded applications in the future.

Abbreviations

ACS	Acute coronary syndrome
AP	Angina pectoris
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
cCTA	Coronary computed tomography angiography
IVUS	Intravascular ultrasound
ICA	Invasive coronary angiography
MI	Myocardial infarction
NPV	Negative predictive value
PCI	Percutaneous coronary intervention
PPV	Positive predictive value
PTP	Pretest probability
TCFA	Thin-cap fibroatheroma

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1 Introduction

Anatomic assessment of the coronary arteries began in earnest in 1958 with Dr. F. Mason Sones's inadvertent injection of contrast material into the right coronary artery of a patient undergoing a diagnostic aortogram (Bruschke et al. 2009). Since then, invasive coronary angiography (ICA) has had a profound effect on the understanding and management of coronary artery disease (CAD). ICA remained the dominant option for the anatomic evaluation of the coronary arteries for nearly 40 years, when rapid advances in computed tomography technology began to produce the temporal and spatial resolution necessary for reliable imaging of the heart and its vessels. The introduction of 64-detector computed tomography systems in 2004 moved coronary computed tomography angiography (cCTA) beyond feasibility testing into clinical practice. Predictably, the abilities and clinical role of cCTA are still evolving. While the high negative predictive value (NPV) of cCTA has provided the basis for endorsement by the major cardiovascular and radiological societies for certain indications, much more high-quality data will be necessary before we can expect a true paradigm shift in the approach to CAD diagnosis and management.

1.1 Basis for Anatomic Imaging of the Coronary Arteries

As this book emphasizes, comprehensive evaluation of the myocardium necessitates much more information than simply identifying and characterizing atherosclerotic disease. Yet assessment of coronary artery morphology plays a major role in establishing a diagnosis, risk-stratification, and therapeutic management in patients with suspected CAD. The current clinical reliance on coronary anatomy is a factor of both pathophysiological and historical factors.

The clinical manifestations of myocardial ischemia can be broadly classified into two categories on the basis of chronicity and underlying pathophysiology—ischemic equivalent chest pain syndrome (angina pectoris or angina equivalent; AP) and acute coronary syndrome (ACS). In both situations, coronary atherosclerosis is the underlying cause in the vast majority of patients. Myocardial ischemia is a result of an imbalance between myocardial oxygen demand and myocardial oxygen delivery. Oxygen demand is a function of heart rate, myocardial contractility, and left ventricular wall stress, which are increased in periods of physical exertion or mental stress. Since myocardial oxygen extraction is nearly maximal at rest, the normal physiological response to increased demand is coronary artery vasodilatation resulting in increased myocardial blood flow. The ability to increase coronary flow over that at rest is termed coronary flow reserve. Atherosclerotic narrowing of the coronary arteries causes a fall in pressure across the stenosis as predicted by the Hagen–Poiseuille equation, with the drop in perfusion across the stenosis inversely proportional to the fourth power of the minimal luminal diameter. Mild stenosis has a negligible hemodynamic effect; however, luminal diameter narrowing above ≈ 50 % causes recruitment of flow reserve at rest (Hendel 2009) resulting in decreased exercise capacity and possibly causing exertional ischemia, clinically manifested as stable AP. At ≈ 80 % luminal diameter narrowing, the coronary reserve is totally recruited at rest, and symptoms of unstable AP may result. This relationship between atherosclerotic coronary artery narrowing and decreased myocardial oxygen delivery forms the basis for anatomic imaging in patients with suspected CAD.

In contrast to stable chest pain syndromes, myocardial ischemia in ACS is usually secondary to sudden rupture of a preexisting atherosclerotic coronary artery lesion, again leading to a mismatch in myocardial oxygen supply and demand. The severity of blood flow reduction will affect the clinical manifestation, ranging from ischemia (unstable AP) to varying levels of myocardial necrosis (myocardial infarction; MI). The likelihood of plaque rupture is more closely related to plaque morphology than stenosis severity (Virmani et al. 2002); however, significant luminal narrowing is detected in nearly all patients with MI at subsequent ICA (Roe et al. 2000), forming the basis for anatomic imaging in cases of acute chest pain/suspected ACS.

Our understanding of the pathogenesis of CAD continues to evolve. While early clinicians worked on the assumption that there was a fairly simple relationship between coronary atherosclerosis and disease manifestation, there is now abundant data showing that the clinical relevance of CAD is related to a host of other factors. Furthermore, correlation between diameter stenosis and functional relevance (likelihood of producing clinically significant ischemia) is suboptimal (see below). The widespread use of ICA over the past half-century, however, has led to abundant data supporting its value. CAD assessment using a simple 1-, 2-, or 3-vessel obstructive disease grading scheme is one of the most important prognostic factors in patients with coronary artery disease, and coronary morphology has been firmly incorporated into clinical guidelines of CAD management, particularly when revascularization is considered (Patel et al. 2012a, b; Smith et al. 2011).

1.2 Limitations

1.2.1 Limitations of Anatomic Imaging

With the advent of new diagnostic tests, such as myocardial perfusion imaging and direct measurements of coronary artery perfusion pressure, we have learned that anatomic imaging results correlate poorly with the functional relevance of disease. It is especially difficult to predict the relevance of intermediate severity lesions (50–70 % stenosis). Many factors outside the coronary arteries have been identified that play a role in myocardial blood flow, including ventricular hypertrophy, microvascular disease, the metabolic state of the myocardium itself, and collateral vessel formation. In addition, the common 1-, 2-, and 3-vessel obstructive disease ranking employed by anatomic imaging tests does not include information on the length of stenoses, plaque morphology, or entrance and exit angles, all of which have been shown to affect pressure gradients (Mark et al. 2010). Anatomic imaging in patients with acute chest pain is also problematic, as ACS is often caused by rupture of a mild/moderate stenosis, with culprit lesions displaying less than 70 % stenosis in up to 80 % of patients with ACS (Roe et al. 2000).

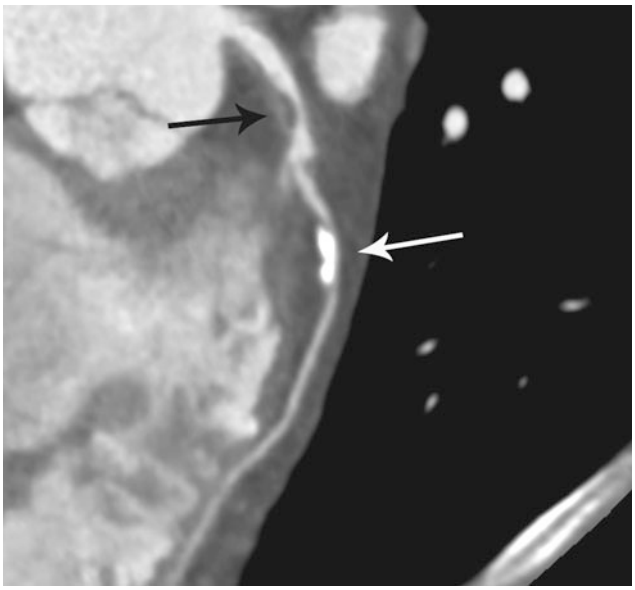

Fig. 1 The degree of stenosis from a distal left anterior descending coronary artery calcified plaque (*white arrow*) is difficult to determine due to blooming artifacts. Compare to the more proximal noncalcified plaque, more easily characterized as causing a 60 % stenosis (Image courtesy of Dr. Stefan Zimmerman, Johns Hopkins Hospital, Baltimore, Maryland, USA)

1.2.2 Technical Limitations of cCTA

Despite advances in cCTA technology, attaining diagnostic-quality studies remains problematic in patients with extremely fast or irregular heart rates (cardiac motion, stair-step artifacts), obese patients (quantum mottle, poor signal to noise ratio), and those who are unable to perform an adequate breath-hold (respiratory motion). While ICA is able to provide temporal resolution of approximately 33 ms, cCTA is currently limited to 75–175 ms. Considering that the translational motion of the coronary arteries ranges from 30 to 90 mm/s at higher heart rates (Lu et al. 2001), some authors have proposed that temporal resolution of 30–50 ms will be necessary for "motion-free" imaging (Lu et al. 2001; Otero et al. 2009). In addition, quantitative imaging of CAD using cCTA remains limited by spatial resolution, with cubic voxels in current scanners ranging from 0.35 to 0.5 mm per edge (Otero et al. 2009) compared with approximately 0.15 mm^3 in ICA. This results in a typical coronary artery (3 mm) being represented by approximately half as many voxels in cCTA compared to ICA (9 vs. 18 voxels, respectively) and precluding the establishment of cCTA as a clinically reliable method for atherosclerosis quantification. Further advances in temporal and spatial resolution should continue to mitigate these limitations.

cCTA evaluation of individuals with high levels of coronary artery calcium has also traditionally been considered problematic. Blooming artifacts can limit assessment of the coronary lumen and result in overestimation of stenosis severity (Fig. 1). A recent meta-analysis, however, found that newer scanners (64-detector and higher) provided high sensitivities and specificities in patients with severe coronary calcifications (den Dekker et al. 2012); in addition, newer acquisition and reconstruction techniques may continue to decrease the impact of coronary artery calcium on the diagnostic accuracy of cCTA (Renker et al. 2011; Schwarz et al. 2012).

1.2.3 Limitations in the Currently Available Evidence for cCTA

There are increasing calls throughout medicine for high-quality evidence establishing the value of diagnostic tests, including cCTA. While the exact methodology for diagnostic imaging validation is not yet established, the evidence required to establish a test as valuable, both on an individual and societal level, generally follows a certain pattern. First, of course, the safety of the test must be established, followed by validation of diagnostic accuracy against a reference standard. The value of prognostic data are increasingly emphasized, as is the ultimate effect on clinical management and outcomes. Finally, the growing economic impact of healthcare throughout the developed world has led to greater emphasis on cost-effectiveness analyses. The quality of the evidence, of course, is also important, with greater weight given to data from large-scale, multicenter randomized trials.

Table 1 Limitations in the currently available evidence for cCTA, stratified by generalized data parameters

Diagnostic accuracy
Most reports consist of single-center studies conducted at academic centers with considerable experience in cCTA, limiting the applicability to mainstream clinical practice
There are limited data for newer techniques utilizing dose-saving techniques; the high diagnostic accuracy seen in most studies is therefore accompanied by relatively high radiation exposure
High variability in treatment of small, highly calcified, or otherwise uninterpretable coronary artery segments; i.e., some studies utilize intent-to-treat designs, others exclude these segments
Technical advancements continue to occur at a rate that quickly renders results obsolete
Anatomic endpoints may be inferior to functional endpoints in guiding patient care
Most studies define "obstructive disease" as stenosis $\geq$ 50 %, and this endpoint is compared to ICA; however, management often relies on the identification of $\geq$ 70 % stenosis
Outcome variables are heterogeneous and may not be clinically validated
Most studies use populations referred for ICA, resulting in inherent referral bias
Asymptomatic patients, acutely symptomatic patients, and/or those with known CAD are variably included and/or combined in analyses, limiting the applicability of data to established clinical indications
Prognosis
Limited large-scale trials currently available
Significant inter- and intra-study heterogeneity in patient populations limits the applicability of data to established clinical indications
CAD classification and reporting are variable and are not limited to standard/recommended clinical practice. In addition, the diagnostic accuracy of more advanced CAD reporting is not well established
Most studies include coronary revascularization as an endpoint, which may not have been warranted or may have been performed as a result of cCTA findings, leading to verification bias
There is low incidence of adverse cardiac outcomes, especially when revascularization is excluded or when all-cause mortality is used as the primary endpoint. Therefore, large cohorts with specific inclusion criteria and long follow-up is required
There are variable risk and prevalence in certain subpopulations (e.g., younger patients (Min et al. 2011), female patients (Shaw et al. 2010), African Americans (Nance et al. 2011), and diabetics (Van Werkhoven et al. 2010))
Economic impacts and effects on clinical management and outcomes
Limited large-scale randomized trials, with data primarily coming from small single-center observational cohorts, larger cohorts utilizing insurance claims data, or simulation models based on prior data
Significant disagreement on the value of different endpoints (for example, cost/quality-adjusted life year, cost/correct diagnosis, incremental cost-effectiveness ratio, etc.)
High variability in patient populations between studies (especially pretest probability) has led to significantly different conclusions
The influence of cCTA utilization on the non-surgical management of CAD is particularly inconclusive from the available data
The effects and optimal management of incidentally detected findings are not well established

Compared to other cardiac imaging techniques, cCTA is relatively young, and this is reflected in the quantity of available evidence. There are limited large-scale trials, especially regarding prognosis, outcomes, and cost-effectiveness. In addition, the data that are available are often subjected to heterogeneous patient populations (which do not clearly reflect the indications set forth in current clinical guidelines), referral bias, and marked variability in experimental design. More detailed limitations in the evidence are provided in Table 1. As such, the clinical role of cCTA is evolving rapidly as new data become available. Fortunately, several large-scale, well-designed trials are underway that should provide considerable value in optimizing cCTA utilization.

1.3 Current Use of Anatomic Data from cCTA

The high NPV of cCTA for the detection of obstructive CAD ($\geq$ 50 % stenosis) forms the basis for currently accepted clinical utilization (Fig. 2). Of note, more advanced characterization of CAD (e.g. quantification, plaque morphological analysis, etc.) is considered experimental at this time. Broadly speaking, cCTA is considered acceptable to detect atherosclerosis in patients with suspected CAD, to rule out significant disease in patients presenting with acute chest pain, to rule out an ischemic etiology in patients without known CAD and new-onset heart failure, for the detection of CAD prior to noncoronary cardiac surgery, and for risk assessment in patients with

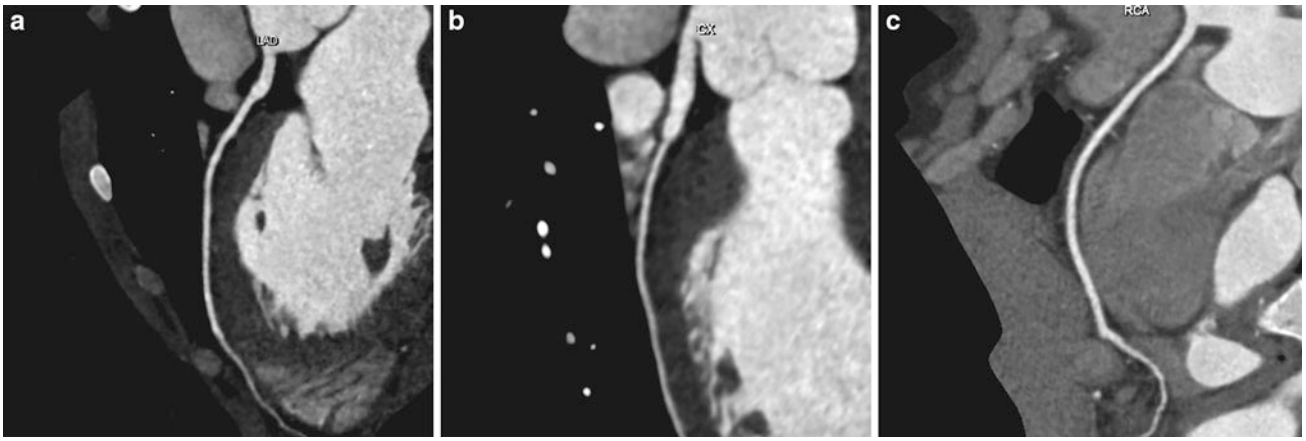

Fig. 2 Normal cCTA shows left anterior descending (**a**), left circumflex (**b**), and right (**c**) coronary arteries without evidence of atherosclerosis (Images courtesy of Dr. Stefan Zimmerman, Johns Hopkins Hospital, Baltimore, Maryland, USA)

prior percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) (Taylor et al. 2010). Optimal integration of cCTA into clinical practice requires the ordering physician to consider all diagnostic and prognostic data available before the test is performed and integrate that information with cCTA results. In addition, the abilities (i.e., high sensitivity) and limitations (i.e., limited positive predictive value) of cCTA must be considered within the clinical situation. Finally, the relative value of alternative diagnostic strategies should be considered in each individual scenario.

The preceding considerations are reflected in the current guidelines for acceptable use of cCTA. The pretest probability (PTP) of disease is an integral component of diagnostic decision-making (Taylor et al. 2010). For example, a patient presenting to the emergency department with acute chest pain and high PTP of significant CAD will likely receive ICA regardless of cCTA results, resulting in increased costs with minimal effect on outcomes or management. Consider, however, a similar patient with low-to-intermediate PTP. The high NPV of cCTA results in the test being well suited to rule out significant CAD in a large proportion of this population, allowing fast, safe discharge (Bamberg et al. 2012). Similar Bayesian techniques should be used on an individual basis for other indications.

2 Technique

There are two basic goals in the acquisition, reconstruction, and interpretation of cCTA examinations: provide maximum diagnostic value while minimizing radiation dose. Newer technologies have increased the quality of anatomic imaging while decreasing ionizing radiation burden; however, proper patient selection, preparation, and post-processing are still vital for optimal performance. This section will highlight the most important considerations and advances in cCTA techniques.

2.1 Patient Selection and Preparation

As noted above, there are multiple patient-specific factors that have a dramatic effect on image quality. Obese patients will require increased tube output for adequate images, and very obese patients should not undergo cCTA. The patients must be able to hold their breath for the duration of the scan, which will be variable depending on the hardware and specific acquisition protocol employed. Patients with very high heart rates or irregular heart rhythms should be carefully assessed and possibly excluded. Preprocedural beta-blocker administration may be used in some cases to reduce heart rate. In addition, some institutions routinely administer nitroglycerin to promote coronary artery vasodilatation and improve image quality. Finally, optimal cCTA acquisition necessitates adequate opacification of the coronary artery lumen; therefore, vascular access must be adequate for high flow rate (4–6 mL/s) administration of intravenous contrast material. Appropriate contrast bolus timing is vital, and both test-bolus and automated bolus tracking techniques can be used.

2.2 Dataset Acquisition

The characteristics of the raw dataset are a major determinate of ultimate image quality. The major parameters influencing the quality of subsequently reconstructed axial 2D images will be spatial and temporal resolution. In addition, detector coverage and acquisition time play a role

in the quality of the examination along the z-axis, affecting subsequent multiplanar and 3D reconstructions. It is important to note that while technical advances are often presented as a solution for a specific imaging parameter (e.g., increased volumetric coverage to improve quality along the z-axis), they usually affect other parameters as well, not always positively.

2.2.1 Temporal Resolution

Temporal resolution is largely a function of the time necessary to acquire a full 360° dataset. As noted above, some authors have proposed that temporal resolution of 30–50 ms will be necessary for true "motion-free" imaging (Lu et al. 2001; Otero et al. 2009). The most obvious method of improving temporal resolution is via faster gantry rotation times, which are now as low as 280–400 ms. However, further improvements will be limited by the mechanical properties of current components, as massive centrifugal forces are generated with such rotational speeds, especially with the increasing mass of wide-detector arrays. Additional techniques to improve temporal resolution include the utilization of half-scan reconstructions (since 360° of data may be acquired with one half gantry rotation). The advent of "dual-source" scanners, containing two sets of X-ray sources and detectors offset at 90°, has allowed further improvement via quarter-scan reconstructions. There are tradeoffs, as both half-scan and quarter-scan reconstruction is subject to misregistration artifacts, and dual-source CT techniques increase X-ray cross-scatter. Multisegment reconstruction, using combined data from adjacent slices, is also available, but has the disadvantage of necessitating decreased pitch, increasing dose, and overall acquisition time. Different commercial products provide specific combinations of these features, and temporal resolution varies accordingly, with the most popular current systems providing resolution of 75–175 ms.

2.2.2 Spatial Resolution

Both intrinsic limitations and reconstruction techniques contribute to the ultimate spatial resolution of cCTA. While spatial resolution is scientifically measured as the minimal allowable distance between 2 structures before they cannot be recognized as separate, voxel size is often used as an indirect surrogate for spatial resolution in cCTA. The x–y lengths are a function of intrinsic CT limitations (e.g., focal spot size and sampling density) and reconstruction techniques, while the z-axis length is largely a function of detector width. As explained above, current voxel dimensions of approximately 0.5 mm^3 are considered adequate for qualitative assessment of the major coronary artery segments but are considered inadequate for quantitative imaging or evaluation of extremely small coronary vessels.

The signal-to-noise ratio, which is related to spatial resolution, is an important consideration as detector widths continue to decrease. Either increased dose, improved reconstruction techniques, or increased detector efficiency will be necessary to maintain adequate photon collection. Technical advances will also be required to compensate for photon loss with improvements in gantry rotation and scan acquisition times.

2.2.3 Volumetric Coverage

The advent of multidetector CT systems, providing increased volumetric (z-axis) coverage with each gantry rotation, was arguably the initial technical advancement that led to the growth of cCTA. While improvements in spatial and temporal resolution have led to improved diagnostic accuracy, the initial feasibility of coronary imaging necessitated full cardiac volume acquisitions in a single breathhold. With increased detectors, fewer rotations of the gantry are necessary to provide complete coverage and total acquisition time is decreased. Continued advancements have led to decreased stair-step artifacts, respiratory motion artifacts, and misregistration artifacts. Faster acquisition times also reduce the significance of heart rhythm abnormalities. Currently, 256- and 320-channel systems have been developed, providing coverage up to 160 mm with a single gantry rotation. These wide-detector systems have made single heartbeat acquisitions a reality. However, while isophasic datasets may intuitively seem attractive, they may not be necessary for anatomic imaging, and the most recent advances in volumetric coverage are driven as much by the prospect of myocardial perfusion imaging as a desire for improved anatomic assessments. Indeed, the wide-cone X-ray beams used for extended z-axis coverage in some systems may come at the expense of decreased spatial resolution from cone-beam artifact, scatter, or roof-top effect. At this time, most of these systems have not been validated as thoroughly as more traditional 64-slice scanners.

Another technique has been introduced to decrease scan acquisition times by using a high-pitch (3.4) spiral acquisition rather than complete cardiac volumetric coverage. This acquisition protocol, which is available in patients with low (< 60 beats/minute) and stable heart rates, can acquire a complete dataset in 250 ms, within one cardiac cycle. The technique also results in very low-radiation dose (Fink et al. 2011).

2.3 Image Reconstruction and Interpretation

Multiple phases of the cardiac cycle will be available following a retrospectively ECG-gated cCTA acquisition. Either automated or manual means should be used to

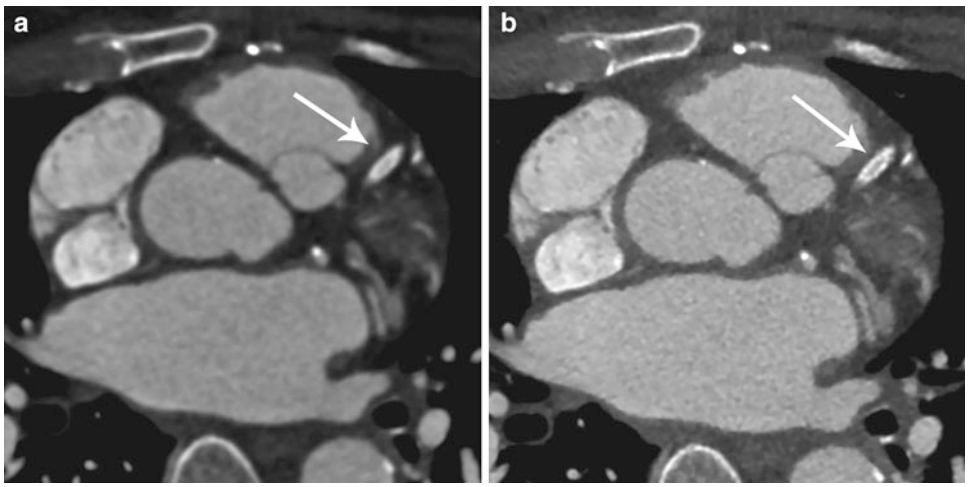

Fig. 3 Filtered back projection reconstruction (**a**) provides inferior spatial resolution compared to iterative reconstruction (**b**) in the assessment of a left anterior descending coronary artery stent (*arrow*) (Images courtesy of Dr. Stefan Zimmerman, Johns Hopkins Hospital, Baltimore, Maryland, USA)

determine the optimal phase for coronary analysis. The appropriate cardiac phase may vary between the left and right coronary circulation. Traditional cCTA dataset reconstruction utilizes filtered back projection techniques; however, there is an increasing interest in iterative reconstruction, which has become more practical with increased computing power. Preliminary data suggest that the greatest role for iterative reconstruction may be in radiation dose reduction, as image quality is maintained at decreased tube currents (Leipsic et al. 2010). Iterative reconstruction may also result in improved image quality (Fig. 3), particularly in the assessment of heavily calcified vessels and stents (Renker et al. 2011).

Most authors advocate the use of several different reconstructions for cCTA anatomical interpretation. Axial images are traditionally used for primary analysis; furthermore, abnormalities seen on additional reformations should be confirmed with axial source images. Multiplanar imaging is available, allowing visualization of the coronary arteries in short- or long-axis, and curved multiplanar reformations allow single-image display of the entire coronary artery length and rotation of the artery along its long axis. Thick-slab maximum intensity projections provide a vascular map, while volume-rendered 3D images allow an overview of coronary anatomy, especially in cases of CABG, but are inadequate for assessment of the coronary artery lumen (Fig. 4).

Computer-aided detection and automated atherosclerosis characterization and quantification programs are becoming increasingly available, and some have shown promising preliminary results (Arnoldi et al. 2009; Blackmon et al. 2009); however, manual assessment remains the mainstay of interpretation at this time. While the current evidence for cCTA is based on relatively simple reporting schemes (similar to ICA), several groups have published studies suggesting the value of more complicated reporting and scoring systems (Chow et al. 2011b ; Kazmi et al. 2011; Min et al. 2007). The Society of Cardiovascular Computed Tomography published a consensus document on cCTA interpretation and reporting in 2009 (Raff et al. 2009a), and we anticipate more guidance and standardization as techniques and data evolve.

3 cCTA in Stable Patients with Suspected CAD

The initial diagnostic evaluation of patients without known CAD presenting with stable chest pain or angina equivalent is complex. Optimizing diagnosis and management of these patients, however, is a major priority considering the scope of the disease and its current and future economic impact. Several strategies are available for initial diagnostic workup, including direct ICA, exercise ECG, exercise and pharmacologically stressed scintigraphy, exercise and pharmacologically stressed echocardiography, and stress magnetic resonance imaging. Anatomic imaging with cCTA has been proposed as a fast, reliable, and possibly cost-effective modality for the initial approach to suspected CAD; in addition, cCTA may have a role as a "gatekeeper" to ICA in certain patients with nondiagnostic or equivocal functional test results.

Currently available evidence on diagnostic accuracy, prognostic value, and effects on outcomes and costs highlight both the advantages and limitations of the technique. Repeatedly, the data show the importance of proper patient selection in order for cCTA to provide cost-effective

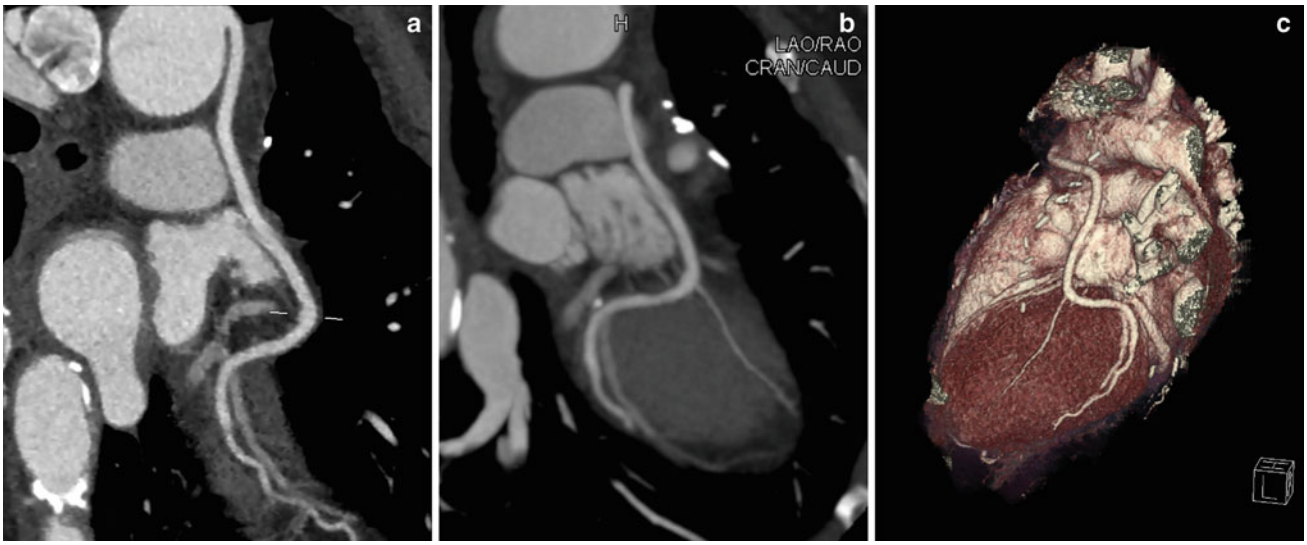

Fig. 4 Curved multiplanar reformation (**a**), thick-slab maximum intensity projection (**b**), and 3D volume rendering (**c**) reconstructions play a role in the assessment of a saphenous vein coronary artery bypass graft to the left circumflex territory (Images courtesy of Dr. Stefan Zimmerman, Johns Hopkins Hospital, Baltimore, Maryland, USA)

therapeutic value. Patient populations with low to intermediate prevalence of disease are most likely to benefit from evaluation with cCTA, while high CAD prevalence increases costs and radiation burden without a positive effect on outcomes.

3.1 Diagnostic Accuracy

Hundreds of studies on various aspects of cCTA diagnostic accuracy have been published over the past decade. As highlighted in Table 1, there are multiple limitations in the available evidence; however, the available data are promising. cCTA consistently shows high diagnostic accuracy to detect obstructive CAD with ICA as the reference standard (Fig. 5). The reported sensitivity and NPV of cCTA are particularly notable, often approaching 100 % in meta-analyses (Mowatt et al. 2008; Sun and Ng 2012). Larger prospective multicenter studies are limited, with only 4 such studies using exclusively 64-slice scanners or higher currently available. Two of the studies include patients with known CAD (Miller et al. 2008) or unstable patients (Meijboom et al. 2008); predictably, the prevalence of CAD was high in these cohorts (56 and 68 %, respectively). Prevalence of 68 % might be expected to negatively impact NPV; however, the authors demonstrated an impressive NPV of 97 %. The other two studies are more applicable in our population. ACCURACY, which included only stable patients being referred to ICA for stable chest pain syndrome and/or abnormal stress test results, had the lowest prevalence of disease, 25 %. Predictable, NPV was excellent in this cohort (99 %) (Budoff et al. 2008).

The positive predictive value (PPV) of cCTA is more limited (ranging from 64–97 % in the 4 prospective studies mentioned above), especially in higher prevalence populations. This could lead to unnecessary, costly, and possibly dangerous subsequent workup, and highlights the need for clinicians to perform robust pretest assessments and order the examination only when appropriate. Further study of cCTA diagnostic accuracy should also increase the evidence comparing cCTA to other noninvasive modalities, such as myocardial perfusion scintigraphy.

3.2 Prognostic Value

The highest-level evidence on the prognostic value of cCTA in stable symptomatic patients uniformly demonstrate the value of cCTA as a rule out test, with a normal scan associated with annualized major adverse cardiac event rates ranging from 0.17 to 0.4 % (Bamberg et al. 2011; Hulten et al. 2011) and all-cause mortality rates ranging from 0.28 to 0.36 % (Chow et al. 2011b; Min et al. 2011). These data support the evidence showing the high NPV of cCTA and compare favorably with other diagnostic strategies, including ICA, myocardial perfusion scintigraphy, and stress echocardiography (Lichtlen et al. 1995; Metz et al. 2007; Shaw and Iskandrian 2004). While the length of protection afforded by a normal cCTA examination is not well-established, one analysis of 1,816 patients with at least 4-year follow-up showed annualized death rates of only 0.22 % (Min et al. 2011), suggesting that 4 years may be a reasonable post-test interval. Current evidence also suggests that there is prognostic value in the detection of obstructive

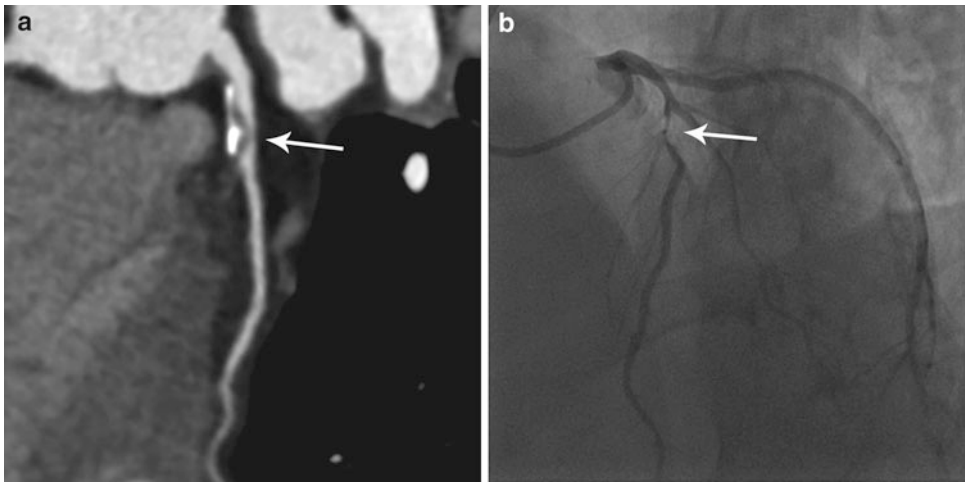

Fig. 5 An obstructive plaque (*arrows*) was detected in the proximal left anterior descending artery on cCTA (**a**), determined to represent an 80–90 % stenosis on subsequent ICA (**b**) (Images courtesy of Dr. Stefan Zimmerman, Johns Hopkins Hospital, Baltimore, Maryland, USA)

disease, with significantly increased rates of major adverse cardiac events (annualized rates up to 11.9 % in one meta-analysis (Bamberg et al. 2011)) and all-cause mortality (up to 2.9 % (Chow et al. 2011b)) in patients with obstructive disease. The prognostic value of more advanced analyses, such as plaque morphology and segmental stenosis scoring, is also being examined and is discussed below in Emerging Applications.

An ongoing goal is to establish the incremental prognostic value of cCTA beyond more established tests. Early data are favorable, with several studies showing increased prognostic value over coronary artery calcium scoring (Bamberg et al. 2011; Hadamitzky et al. 2011) and myocardial perfusion scintigraphy (Shaw et al. 2008; van Werkhoven et al. 2009). In addition, researchers are seeking to refine the population-specific prognostic value of cCTA, e.g., in younger patients, females, or diabetics.

3.3 Outcomes and Costs

There are substantial methodological weaknesses in all of the currently available data on outcomes and costs of cCTA in stable symptomatic patients; however, two large-scale randomized clinical trials are currently underway. The RESCUE trial will compare cCTA to myocardial perfusion scintigraphy in 4,300 patients with stable angina or angina equivalent and the PROMISE trial will compare cCTA to traditional stress testing (ECG, echocardiography, or scintigraphy) in 10,000 symptomatic patients with low to intermediate PTP of CAD. Both studies will follow patients to compare outcomes and costs.

Until then, we must rely on the available observational cohorts and simulation models, which currently suggest that cCTA provides incremental cost-benefit (cost/correct diagnosis) and cost-effectiveness (cost/quality adjusted life year) compared with alternative strategies in populations below a certain prevalence of disease. These data are variably driven by improved outcomes using cCTA-based strategies (Ladapo et al. 2009), decreased costs (Dorenkamp et al. 2011; Genders et al. 2009; Min et al. 2008a), or some combination. Importantly, no current data have shown adverse outcomes when cCTA is used. cCTA has not been shown to be cost-effective in populations with PTP greater than 37–55 % (Dorenkamp et al. 2011; Genders et al. 2009) or disease prevalence greater than 30–50 % (Min et al. 2010; Shreibati et al. 2011) due to high downstream resource utilization (particularly subsequent ICA) (Min et al. 2008a; Shreibati et al. 2011). Of note, real-world observational studies have shown decreased downstream resource utilization following clinical cCTA implementation, possibly due to more appropriate patient selection and clinical management (Karlsberg et al. 2010).

4 cCTA in Patients with Acute Chest Pain

The workup and triage of patients presenting to the emergency department with acute chest pain represents a common and difficult diagnostic dilemma across the developed world. While ECG, clinical decision rules, and sensitive cardiac biomarkers are available and can lead to rapid triage to ICA in a minority of cases, greater than 80 % of patients have a nondiagnostic initial workup and require either serial clinical and laboratory monitoring or additional testing (Anderson et al. 2007). Furthermore, approximately 80 % of those patients will eventually receive a diagnosis of non-cardiac chest pain (Roger et al. 2012), and a small but concerning percentage of discharged patients actually have ACS. The process is not only expensive but also results in a significant diversion of resources as patients are monitored or prepared for time-consuming tests such as cardiac

scintigraphy. The speed and excellent NPV of cCTA form the basis for its utilization in these situations, with the primary goal of providing safe, rapid discharge for the large percentage of patients without ACS.

4.1 Diagnostic Accuracy and Prognostic Value

Many studies have been published on the diagnostic accuracy of cCTA; however, studies encompassing only patients presenting to the emergency department with acute chest pain and low to intermediate PTP of ACS are more limited. Nevertheless, early data again suggested that cCTA is very reliable in excluding CAD. Recently, more robust data have emerged that again displays the excellent NPV of cCTA for the detection of patients with ACS. Importantly, and in contrast to diagnostic studies in which other imaging is used as the reference standard, these investigations have used index hospitalization and follow-up data to determine positive findings (i.e., ACS) and calculate diagnostic accuracy and prognostic value.

One of the first large prospective observational studies evaluating cCTA in the setting of acute chest pain was the ROMICAT trial, which enrolled 368 patients with low to intermediate risk. The NPV of cCTA in the detection of any CAD (50 % of the subjects) was 100 %, while the NPV was 98 % when cCTA detected CAD but no significant stenoses (Hoffmann et al. 2006). Three multicenter randomized controlled trials have been performed that displayed similar data, all enrolling patients with low to intermediate PTP presenting to the emergency department with acute chest pain. The CT-STAT trial randomized 699 patients to either cCTA or myocardial perfusion scintigraphy and found no difference in adverse events after 6 months (Goldstein et al. 2011). The ROMICAT II trial randomized 1,000 patients to either cCTA or standard evaluation and demonstrated a 100 % NPV for cCTA in the exclusion of ACS. In addition, there was no difference in major adverse cardiac events between the two strategies after 28 days (Hoffmann et al. 2012). A 2012 study randomizing 1,370 patients to cCTA or standard care also showed the value of negative cCTA examinations, with zero deaths or MIs after 30 days in the 640 patients with a negative study (Litt et al. 2012).

As before, the PPV of cCTA in these situations is much more limited, hence the evolution of the test into a largely "rule-out" role. In addition, the ability of cCTA to detect functional stenoses in these patients is also limited; however, this fact per se does not undermine cCTA's value as a rapid triage test.

4.2 Outcomes and Costs

The importance of proper patient selection is again emphasized in cost-effectiveness data for cCTA utilization in the emergency department. Several of the large observational studies presented in Sect. 3.3 included patients with acute chest pain, and some of the conclusions can justifiably be extrapolated to this population. Namely, patients with a high risk of ACS or CAD should not undergo cCTA, as downstream ICA utilization will be high and drive up costs without outcome benefits. Model-based analyses specific to the acute chest pain setting have shown cCTA-based strategies can be more cost-effective than stress ECG, stress echocardiography, and myocardial perfusion scintigraphy under certain conditions, including disease prevalence <70 % (Khare et al. 2008; Ladapo et al. 2008).

Fortunately, the randomized controlled trials mentioned above have also provided fairly robust data on the potential value of cCTA. While the CT-STAT trial demonstrated a 38 % cost savings per patient in the cCTA arm, ROMICAT II found no differences in cumulative per-patient costs between cCTA and traditional care. Importantly, however, there is strong data pointing to several other benefits of a cCTA-based approach. CT-STAT demonstrated a 54 % reduction in the time to diagnosis when cCTA was used, while ROMICAT II and the study by Litt et al. showed significant decreases in total length of stay compared to traditional care (median 8.6 vs. 26.7 and 18.0 vs. 24.8 h, respectively). In both of the latter studies, nearly half of patients undergoing cCTA were discharged directly from the emergency department, compared to 12–23 % of those patients in the standard care arms. Litt et al. also showed that while there was no difference in rates of subsequent ICA, patients who had undergone cCTA were more likely to have positive ICA findings, suggesting that cCTA may lead to more appropriate clinical decision-making.

5 Other Indications

5.1 Evaluation of Patients with New Heart Failure

The differentiation of ischemic cardiomyopathy from non-ischemic dilated cardiomyopathy, the two major causes of heart failure in the developed world, has important prognostic and management implications. Perhaps most importantly, patients with systolic dysfunction secondary to CAD may be amenable to revascularization. As such, ICA is employed in the diagnostic workup of certain patients with

new-onset or newly diagnosed heart failure. cCTA may represent a noninvasive alternative to ICA in some patients, especially considering its high NPV, and current guidelines consider cCTA use acceptable in patients without known CAD with low or intermediate PTP (Taylor et al. 2010). The justification for this is largely based on broader studies, with only limited population-specific evidence. However, the little data that are available are generally favorable, with sensitivities and specificities ≥ 90 % for the detection of CAD or ischemic heart disease. Furthermore, one small prospective study found that all patients with a negative cCTA examination could avoid ICA, suggesting some cost benefits (Ghostine et al. 2008; Hamilton-Craig et al. 2012). Further evaluation on prognosis, outcomes, and costs will be necessary to refine the role of cCTA in this situation.

5.2 Patients Prior to Noncoronary Cardiac Surgery

ICA is widely utilized prior to noncoronary cardiac surgery, especially valvular surgery, and is considered acceptable in this situation by current practice guidelines (Patel et al. 2012a). Again, cCTA may offer an attractive alternative in this situation, but population-specific data are limited. Several studies have shown high diagnostic accuracy in preoperative coronary evaluation (Mark et al. 2010); furthermore, two studies examining outcomes have shown that cCTA is safe, with one study finding no MACE in the perioperative period or at 3 month follow-up in patients with a negative cCTA (Buffa et al. 2010) and another study finding no difference in operative mortality or postoperative MI between patients who had received cCTA compared to those who had received ICA (Nardi et al. 2011). Again, the value of cCTA may lie in its ability to prevent unnecessary catheterization in a large number of patients. Of the two studies mentioned above, 81–85 % of patients undergoing cCTA had negative examinations and were able to safely avoid ICA.

5.3 Patients with Coronary Artery Stents

In-stent restenosis remains a considerable problem in modern cardiology practice. Unfortunately, there are several limitations associated with cCTA stent evaluation, and current guidelines consider cCTA acceptable only in the evaluation of left main coronary artery stents ≥ 3 mm in asymptomatic patients (Taylor et al. 2010). The main problem involves poor image quality rendering a significant proportion of stents unevaluable. High-density stent material is subject to beam-hardening and blooming artifacts, and partial volume averaging can result in artificial luminal narrowing of up to 60 %. The percentage of unevaluable stents varies widely between reports; however, even with specialized reconstruction techniques, at least 8 % of stents cannot be reliably assessed with current scanners (Mahnken 2012). Various parameters have been associated with stent evaluability, including strut thickness, stent location, and stent material; however, the strongest evidence points to stent diameter as the most important parameter, with accessability rates varying from 100 % in stents ≥ 3.5 mm to 33 % when diameter is <3 mm (Sheth et al. 2007).

Of note, meta-analyses have shown that the diagnostic accuracy of cCTA is quite good when only assessable segments are considered, with pooled sensitivities and specificities of 86–90 % and 91–93 %, respectively. However, including nonassessable segments decreased both parameters to around 80 % (Carrabba et al. 2010; Sun and Almutairi 2010). Interestingly, one study has compared stent assessment with ICA and cCTA using intravascular ultrasound (IVUS) as the reference standard and demonstrated a higher diagnostic accuracy with the use of cCTA (Hang et al. 2011). This raises questions regarding the reliability of prior diagnostic data comparing cCTA with ICA as the reference standard.

5.4 Patients with Prior CABG

Currently available evidence has been deemed adequate to justify the use of cCTA in the assessment of symptomatic patients who have had prior CABG (Taylor et al. 2010). Symptoms may result from flow-limiting lesions in ungrafted native arteries, native arteries distal to graft insertion, the proximal and distal anastomoses, or the grafts themselves. cCTA has shown good diagnostic accuracy in the assessment of grafts, with overall sensitivity and specificity ≥ 97 % to detect graft occlusion or significant stenosis (Hamon et al. 2008; Stein et al. 2008). Predictably, accuracy is higher in the detection of occlusion compared to stenosis and when assessing venous versus arterial grafts (secondary to the smaller size and increased adjacent surgical clips associated with arterial grafts). However, cCTA is somewhat limited in the assessment of distal anastomosis sites and, perhaps more importantly, the native coronary arteries (Fig. 6). Studies have shown that as many as 9 % of native arteries (both ungrafted and distal to graft insertion) are unevaluable, largely due to small size and high burden of dense calcifications. Furthermore, diagnostic accuracy is reduced when assessing native coronary arteries of prior CABG patients compared to those who have not undergone CABG, even among exclusively evaluable segments (Ropers et al. 2006). Despite these limitations, cCTA appears to be a viable alternative to ICA. Recent studies evaluating prognostic value have strengthened the evidence