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REVIEW

CARDIAC COMPUTED TOMOGRAPHY
THE DATA AND EVOLVING APPLICATIONS

Dual energy cardiac computed tomography

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ABSTRACT

Conventional single energy CT suffers from technical limitations related to the polychromatic nature of X-rays. Dual energy cardiac CT (DECT) shows promise to attenuate and even overcome some of these limitations, and might broaden the scope of patients eligible for cardiac CT towards the inclusion of higher risk patients. This might be achieved as a result of both safety (contrast reduction) and physiopathological (myocardial perfusion and characterization) issues. In this article, we will review the main clinical cardiac applications of DECT, that can be summarized in two core aspects: coronary artery evaluation, and myocardial evaluation.

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During the past decades, cardiac computed tomography (CT) has rapidly gained an active role in diverse clinical scenarios. Nonetheless, conventional single energy CT (SECT) still suffers from a number of technical limitations related to the polychromatic nature of X-rays, such as beam hardening artifacts (BHA) and blooming artifacts. These artifacts degrade the interpretation of both CT coronary angiography (CTCA) and CT perfusion (CTP) studies, increasing the false positive rate and thus potentially leading to increments in downstream testing. In parallel, safety issues such as contrast induced nephropathy (CIN) preclude CTCA among high risk patients.

Dual energy cardiac CT (DECT) shows promise to attenuate and even overcome some of the aforementioned limitations. The first descriptions of DECT, also known as spectral CT, date back to more than three decades ago.[1] At those days two separate scans were required for this purpose, thus it was not possible to achieve adequate colocalization and contrast and tissue differentiation. Furthermore, until recently, DECT was not clinically available due to technical limitations regarding limited temporal and spatial resolution as well as high image noise and radiation dose issues. This technique offers the potential to evaluate the chemical composition of different tissues in relation to the atomic composition.

With the advent of dual source CT, cardiovascular DECT became feasible, and the first clinical applications for this system emerged.

In this article, we will review the main clinical cardiac applications of DECT, that can be summarized in two core aspects: coronary artery evaluation, and myocardial evaluation.

Fundamental principles and technical requirements

The basic requirements to perform dual energy/spectral CT are the following:

— X rays sources providing x rays quanta with different energies;

— detector technology able to differentiate diverse quanta at dissimilar energies;

— tissues with sufficient difference of the materials densities on diverse energies.

Attenuation of tissues measured in CT is characterized by three physical processes: 1) Compton scatter, which is the largest component of attenuation in relation to electron density, 2) Rayleigh scatter, related to the electrons but only constitutes a minimum amount; and 3) photoelectric effect which is closely related to the atomic number z of the material (number of protons of the atomic core).

Tissues with significant differences in Z values might be differentiated by spectral properties.

The elements that work best with DECT are those with high atomic number. Accordingly, elements such as iodine (z=53) and calcium (z=20) have significantly different behavior between low and high energy levels, whereas elements with low atomic number such as hydrogen (z=1), oxygen (z=8), carbon (z=6) and nitrogen (z=7) show no signifincat differences across the spectral range.

Currently, there are three CT scanners capable of generating two X-ray beams of low and high energy:

— dual-source CT scanner with 80 (100) kVp and 140 kVp tubes (Siemens Medical Solutions, Erlangen, Germany);

— dual-layer -detector scanner with acquisition at 120 or 140 kVp (Philips Healthcare, Amsterdam, The Netherlands);

— CT unit with single source rapid kVp switching and new detector based on gemstone scintillator materials (GE Healthcare, Chicago, Illinois, USA).

Dual-source CT

A dual/source CT (DSCT) is a CT scanner with two x-ray tubes and two detectors attached onto the rotating gantry with an angular offset of 90°. Both structures run simultaneously and attain CT scan data at the identical anatomical position of the patient (same z-position). This approach had three generations since its introduction. The latest advance was attained with the integration of the SOMATOM Force in 2014 which permitted a second SFOV of 35.5 cm, 196 overlapping slice acquisition and

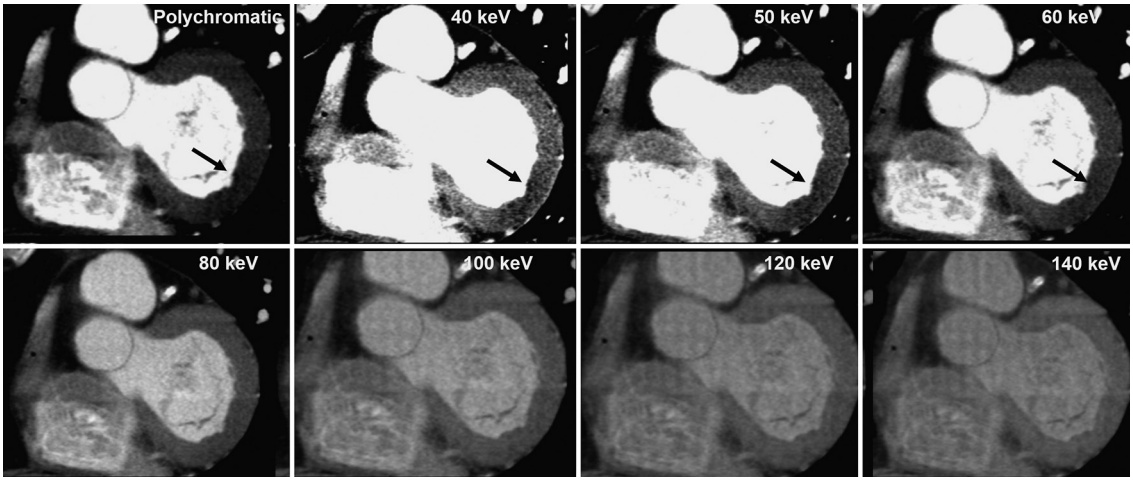

Figure 1.—Basal inferolateral myocardial hyoattenuation in a patient without coronary artery disease. Beam hardening artifact progressively declines at incremental energy levels, with homogeneous myocardial signal density levels at mid to high energy levels. Polychromatic images (single energy-like) are also depicted, showing a inferolateral myocardial hypoattenuation.

gantry rotations of 0.25 s. Also temporal resolution has been optimized from 83 msec up to 66 msec from 1st up to 3rd generations. Other benefits of this scanner consist of an additional beam filter that can be added to one tube to further separate the energy spectra of low- and high- energy beams.

Dual layer detector CT scanner

The dual-layer detector CT scanner has a single x-ray tube that works with a peak tube potential alternating from 80-120 kVp. The detector is constituted by 2 layers of diverse scintillator material placed one on top of the other. The topmost layer is composed of zinc selenide and absorbs photons in the low energy range while the lowermost layer of orthosilicate absorbs the residual higher energy photons giving an exact spatial and temporal registration of data sets. First generations of this approach allowed 64 slices of 0.625mm thickness and gantry rotation time of 270 msec.

CT unit with one rapid kVp switching source

This scanner has a single X-ray tube voltage generator with a rapid kV switching acquisition protocol that quickly shifts between low (80) and high (140) kV settings from one projection view to the next in less than a millisecond (GE Healthcare CT750 HD scanner and the newer Revolution scanner). The tube voltage generator must deliver a voltage waveform that has a short rise and fall time to diminish the contamination between the low and high signals in adjacent views.

DECT image output

DECT can generate diverse types of images for various clinical applications such as conventional polychromatic, virtual monochromatic, and material decomposition.

Polychromatic images

These images are obtained from the initial acquisition of a dual energy CT scan. They resemble single energy CT images.

Virtual monochromatic images

In order to create virtual monochromatic images (VMI) two basic materials such as iodine and water are required. Attenuation measurements transformed into densities obtained from low and high kilovolt peak projections are calculated and then rebuilt to originate the base material image pairs. Monochromatic analysis allows the visualization of the anatomy at different energy levels ranging from 40 to 140 keV (Siemens and GE) and up to 200 keV (Philips). Low energy levels demonstrate higher intraluminal enhancement, allowing a significant reduction in iodinated contrast load for cardiovascular CT, although at the expense of increased image noise. Notwithstanding, this limitation will be attenuated with the recent incorporation of iterative reconstruction techniques also available for low energy levels (previously available only for ≥60 keV).

Mid energy levels ranging from 77 to 100 keV have been shown as the the best to attenuate or cancel common artifacts that affect single energy CT such as blooming and BHA. Blooming artifacts exaggerate the size of calcified plaques, leading to stenosis overestimation in cases of severe calcification. In turn, as aforementioned, BHA typically appear in sites where two adjacent structures with high density suffer from material inhomogeneity, and can result in false perfusion defects in certain myocardial segments such as posterobasal (American Heart Association segment 5) and apical segments (Figure 1).

Finally, high energy levels "subtract" the iodinated contrast from the vessels and organs leading to images without contrast, also known as "virtual non-contrast images" (VNC). These type of images can lead to radiation dose reduction as they might avoid true non-contrast phases.

Material decomposition

Material decomposition (MD) is based upon different attenuation coefficients of several tissues that depend on the energy levels of the X-ray beam. MD harvests information about tissue atomic number and can provide maps in

relation to certain basic tissues such as water or iodine, allowing measurements of the concentration of a selected tissue in a given voxel (mg/mL). Currently, DECT admit choosing tissue pairs where the first tissue will be kept in the image while the second one will be subtracted. Many pairs can be generated, being the most useful for cardiovascular purposes the following: iodine-water (iodine is kept and can be measured, water is cancelled), iodine-calcium (iodine is preserved, calcium is withdrawn), and calcium-iodine.

Iodine-water pair can be used for myocardial perfusion evaluation, allowing measurements of the normal or abnormal concentration of iodine in the myocardial wall. Iodine-calcium permits to take out the calcium of the wall of the arteries helping in the stenosis assessment. Finally, the calcium-iodine pair might lead to reduction in radiation dose by eliminating iodine from the lumen, therefore avoiding the acquisition of a separate non-enhanced calcium score scan in order to estimate coronary artery calcium scoring (CACS).

Clinical applications of DECT

As aforementtioned the cardiac clinical applications DECT will be classified in the evaluation of two regions: coronary arteries, and myocardial wall.

Coronary arteries

DECT can offer potential benefits over SECT. Among the advantages, some already established and other under evaluation, we can mention:

— iodinated contrast load reduction;
— improved stenosis quantification;
— improved plaque characterization;
— radiation dose reduction;
— CACS from contrast-enhanced scans.

Contrast reduction

As abovementioned, monochromatic analysis at low energy levels provides higher intraluminal enhancement enabling a significant reduction in the iodinated contrast load. This distinctive feature of DECT has yield positive results in various vascular territories such as the aorta, pulmonary arteries, carotids, and even coronary arteries.

Contrast reductions of up to 60% of iodine volume have been shown, with comparable image quality and assessibility than CT angiography with full iodine load using conventional SECT.

Despite the incidence of CIN is very low in patients with normal renal function, the risk of CIN is significantly higher in patients with established risk factors such as diabetes, heart failure, peripheral vascular disease, and anemia.[2] Besides, the most important risk factor related to CIN is the total iodinated contrast volume load. Therefore, is is critical to encourage strategies aimed at reducing iodine load (either reducing contrast volume or concentration), not only for patients at risk of CIN but also for those with normal creatinine levels, in whom it has been documented underlying subclinical renal dysfunction in up to 20%. As a matter of fact, an incidence of CIN of 11 % has been reported associated to contrast-enhanced CT in the outpatient setting.[3]

Furthermore, it has been previously shown that in patients with established renal disfunction, each additional 20 mL leads to a twofold increase in risk of CIN.[4] Our group has reported up to 70% reduction in contrast iodine load (up to 60% with good image quality) in aortic CTA, leading to studies with as low as 30 mL.[5] It has been hypothesized that such exceedingly low volumes might be used even in patients with renal failure.[6]

Regarding the coronary territory, CTCA using DECT has allowed up to 50% reduction in contrast volume, with comparable image interpretability and diagnostic performance than SECT using full iodine load (Figure 2).[7]

Better stenosis quantification

CTCA has consitently been established as an accurate non-invasive tool to assess the presence and extent ot coronary atherosclerosis, not only of the lumen (as invasive coronary

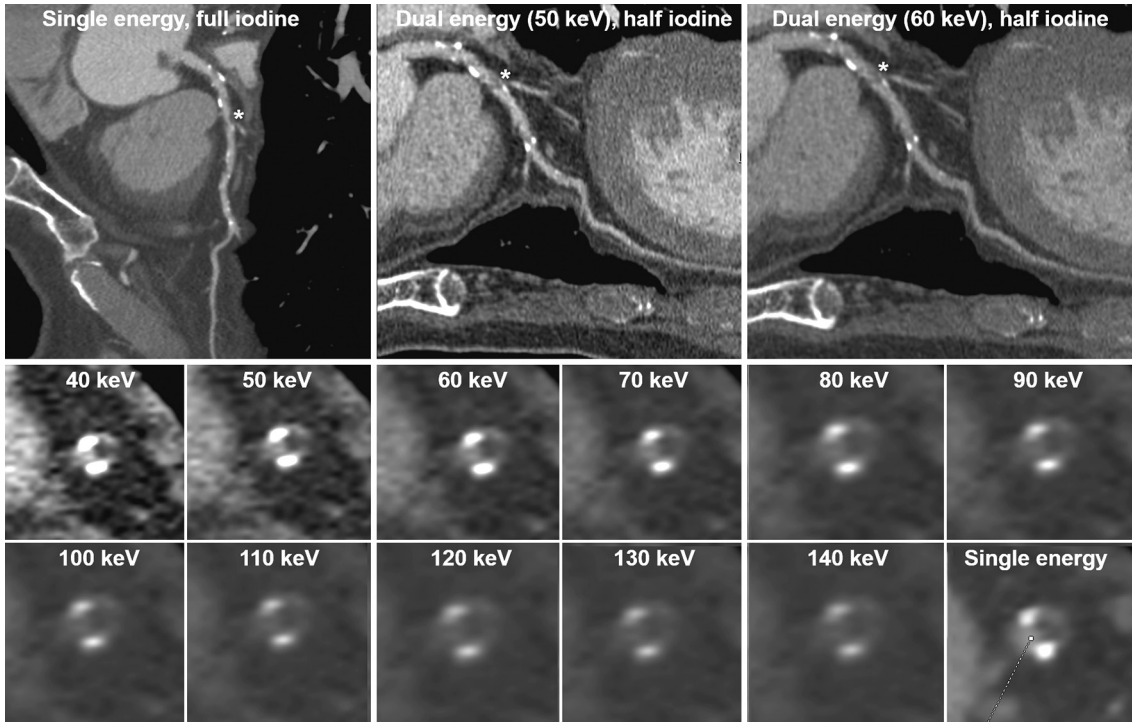

Figure 2.—Curved multiplanar reconstruction of a left anterior descending artery (LAD) acquired using single energy CT at full iodine load, and dual energy CT at half iodine load. A significant mixed lesion (*) is observed at the the proximal LAD, similarly depicted with both strategies. Orthogonal views at increasing energy levels and using single energy CT are also depicted.

angiography, ICA) but also of the vessel wall. Indeed, CTCA is related more closely to intracoronary ultrasound than to ICA. The diagnostic perfomance of conventional (single energy) CTCA in patients with no or mild to moderate calcification of the coronary tree is high, with a particularly high negative predictive value. Nonetheless, evaluation of patients with moderate to severe calcification poses a challenge for this technique, in part attributed to blooming artifacts that lead to overestimation of calcified plaque volume (Figure 3), often generating innacurate stenosis quantification. In fact, an ancillary analisis of the CORE-64 study reported a positive likelihood ratio (LR +) of 34.4 (95% CI 23.1, 51.2) for the evaluation of non-calcified segments, compared to a LR+ of 9.9 (95% CI 7.5, 13.1) among mildly calcified segments, of 4.3 (95% CI 3.3, 5.5) among moderately calcified segments, and of 2.8 (95% CI 2.2, 3.5) among segments with severe calcification.[8] For this reason, indication

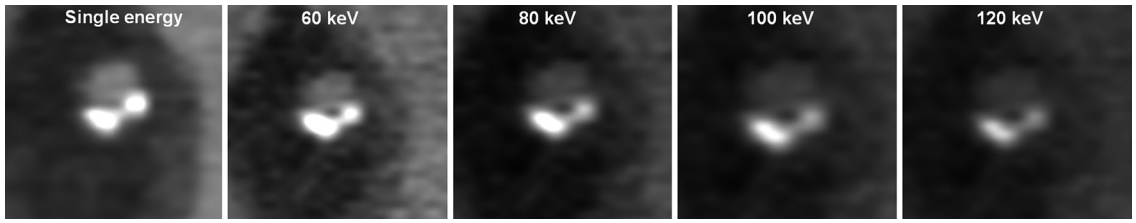

Figure 3.—Orthogonal views of a non-significant lesion at the left main coronary artery of the previous patient. A calcified plaque from 3 to 9 o'clock is observed at single energy CT. Dual energy CT at high energy levels demonstrate very mild calcification.

of SE-CTCA has been restricted to patients with low to intermediate probability of CAD. Patients with intermediate to high pre-test of CAD are generally associated with diffuse calcifications, resulting in low positive predictive value of this technique.

By virtue of virtual monochromatic analysis at mid energy levels, DE-CTCA shows promise to attenuate this limitation of CTCA (Figure 3). Mid energy (77-100 keV) levels have shown to significantly reduce blooming artifacts, enabling more precise calcified plaque area measurements, and consequently a more precise stenosis assessment.

A number of studies have compared calcified plaque measurements between DE-CTCA and histopathology. In one of these studies, Mannelli *et al*. evaluated five *ex vivo* endarterectomies with DE-CTCA and histology. A total of 107 matched sections were evaluated with DE-CTCA (using monochromatic exploration at different energy levels) and histopathology. No significant differences were detected between the calcified areas measured by histology and those by DE-CCTA at energy levels ranging from 77keV and 100 keV.[9]

Few in-vivo studies have explored the promising role of DE-CTCA for the assessment of CAD. Scheske *et al.*, using higher energy levels, demonstrated a significant reduction of high-attenuation artifacts.[10]

Our group has recently reported the diagnostic performance of single-source ultrafast kV switching DE-CTCA in 67 patients with intermeadiate to high likelihood of CAD. In this study DE-CTCA using energy levels from 65 to 85 keV showed a good diagnostic performance among patients with moderate coronary artery calcification scores. Furthermore, patients with moderate calcification showed a trend towards improvement in diagnostic performance with mid energy (65 keV) *vs*. low energy (45 keV) reconstructions (P=0.06). Nevertheless, patients with diffuse calcification had significantly lower diagnostic performance compared to segments with none or mild calcification, regardless of the energy level.

Another important previous concern has been addressed with the recent software improvements, iterative reconstruction is now available also at the lowest energy levels, which are particularly noisy. It is important to combine DE-CTCA with the application of iterative reconstruction. This has been tested in the study of Fucks *et al*., where the authors explored 35 different combinations of energy levels (60 keV, 65 keV, 70 keV, 75 keV, 80 keV, 90 keV, and 110 kV) and ASiR (at 0%, 20%, 40%, 60%, and 80%). All monocrhomatic images were compared with standard polychromatic images (standard reconstructions). Compared with standard images, 60 keV with 80% ASiR combination was the one that showed the highest contrast-to-noise and signal-to-noise ratio. However, image quality reached a plateau at 65-to75 keV with 40-60% ASiR, with 50% quality improvement versus standard images (P<0.001).[11]

Another improvement that might aid a more precise stenosis quantification is applying MD with the pair iodine-calcium, where iodine is maintained in the image while calcium is removed, leading to a non-calcim luminogram. This tool is complementary and may help in the diagnosis although evidence in this regard is scarce.

Better plaque characterization

A large number of studies have demonstrated the ability of CTCA to evaluate the coronary vessel wall aside from the lumen, being able to determine not only the degree of stenosis but also plaque chacteristics.

Indeed, CTCA can identify various characteristics associated to high risk plaques such as positive remodeling (which is directly related to the extent of lipidic-necrotic core), spotty calcifications, and other high risk features related to thin-cap fibroatheroma such as the napkin-ring sign and low-attenuation plaques.

SE-CTCA can differenciate calcified from non-calcified plaques with high sensitivity and specificity, although it usually suffers from a substantial tissue density overlap in a certain range leading to a relatively poor discrimination between soft and fibrous tissue. Such discrimination is of foremost importance since these components that constitute non-calcified

plaques cannot be adequately discriminated by SE-CTCA.

DE-CTCA opens a new possibility for plaque evaluation, with a potentially improved discrimination of plaque components and lesser overlap of tissue densities. The potential role of DECT for this purpose seems to be linked to the fact that by means of x-ray imaging at different energies, attenuation values of key plaque components such as fibrous tissue and necrotic core might have individual behavior. The ability of DECT imaging to discriminate the composition of kidney stones and tumors shows promise in this regard.

Obaid and collegues evaluated the role of DE-CTCA in determing atherosclerotic plaque characteristics in 20 patients using intravascular ultrasound radiofrequency data analysis as reference standard, and in 7 explanted coronary arteries. The authors explored the attenuation (HU) thresholds that best identified necrotic core tissue using SE-CTCA and DE-CTCA (using dual-energy indices, defined in this study as differences in HU at the 100 and 140 kV/their sum). DE-CTCA showed improved diagnostic accuracy to detect necrotic core in postmortem arteries compared to SE-CTCA, applying a DEI threshold <0.016 DE-CTCA achieved a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 64%, 98%, 95%, 87% and 85%, respectively. It is noteworthy that DEI ranges for necrotic core (-0.001 to 0.016) did not overlap with any other tissue, whereas both single energies showed a marked overlap between necrotic core and fibrous tissue ranges (100 kV 37-219 HU; 140 kV 39-121 HU). However, the *in-vivo* diagnostic accuracy for the identification of necrotic core was suboptimal, and DE-CTCA had lower image quality than SE-CTCA, despite DE-CTCA showing modest improvements in diagnostic accuracy compared to SE-CTCA.[12]

It is noteworthy that the diagnostic performance of CTCA for plaque characterization might be higher at lower energy settings (80 kV). This has been recently shown in an *ex vivo* study, where the area under the curve for the discrimination between lipidic and fibrotic plaques was 0.81 for 80 kV, 0.77 for 100 kV, 0.68 for 120 kV, and of 0.65 for 140 kV.[13]

Finally, future studies should certainly explore the potential role of DE-CTCA at low energy levels for the assessment of delayed enhancement as a correlate of plaque neovascularization and intraplaque hemorraghe.[14] In addition, DE-CTCA at low energy levels might aid the assessment of differences in signal densities from the early (first pass) to the delayed (late enhancement) phase, since this approach has shown potential to discriminate between necrotic core and fibrous tissue.[15]

Radiation dose reduction

During the early years of the technique, DE-CTCA was related to high radiation dose, particularly associated to dual source DE-CTCA. However, a number of technological developments have enabled a considerable reduction in radiation doses to levels similar or even lower than with SE-CTCA.

According to the type of scanner used, the combined use of low and high tube power works different. In the case of dual source CT, the two tubes operate simultaneously at a full power dose each. On the other hand, in the single source kVp-switching approach one tube drives at low (80kV) and the other at high (140kV) potential with an ultrafast switching, leading to a mean tube power of 110 kV in this setting.

An important benefit of using spectral range is the opportunity to subtract completely the contrast from vessels and organs at high levels. In those levels images are shown without enhancement simulating non-contrast scans. For that reason, contrast-enhanced images evaluated at high energy levels are known as virtual non contrast, and may admit to avoid the true non-contrast scans thus reducing the overall radiation dose to the patient.

CACS from contrast-enhanced scans

Different investigators have explored the possibility of avoiding true non-contrast scans and in the context of cardiac imaging this allows obtaining CACS from a DE-CTCA.

Although the radiation dose of conventional CACS is low, it might be completelly avoided if this information could be obtained using monochromatic information at high energy levels. Another possiblity to measure CACS from a contrast-enhanced scan is by applying MD with calcium-iodine pair, thereby sustracting iodine. In both scenarios the prognostic information of CACS can be assessed, allowing both prognostic and diagnostic information obtained from a single acquisition.

Myocardial evaluation

The potential clinical applications of DECT in the context of the evaluation of the myocardial wall are mainly related to myocardial perfusion, and infarct characterization.

Myocardial perfusion

During the past years SE-CTCA emerged as a the mostly seeked potential one-stop-shop non invasive diagnostic tool, with the ability to evaluate both coronary anatomy and functional assessment in a single session. Numerous clincal studies performed on 64, 128, 256 and 320-row scanners have demonstrated the feasibility and high diagnostic accuracy of CT myocardial perfusion (CTP), using diverse techniques as reference standard. Furthermore, last year two multicenter trials have confirmed earlier findings in a larger scale. Despite SE-CTCA has consistently demostrated good results for CTP, due to the polychromatic nature of the x rays this technique is affected by BHA that commonly generate areas of hypoattenuation that can mimic hipoperfusion in certain myocardial segments (Figure 1). For that reason DECT offers the potential to overcome technical limitations such as BHA (Figure 4). The potential of DECT in this regard is related to the ability to enable virtual monochromatic examination and MD.

The first publications addressing the role of DECT in cardiac imaging were mainly focused at CTP. In the study of Ruzsics *et al.*, that comprised 36 patients with equivocal SPECT studies who also underwent dual energy CTP imaging using a dual source first generation CT scanner, the technique had a sensitivity of 92% and a specificity of 93% for the detection of perfusion defects.[16] In parallel, similar findings were reported in other study using adenosine stress DECT compared to perfusion magnetic resonance imaging, showing a sensitivity of 89% and a specificity of 78% for the detection of reversible perfusion defects in 50 patients.[17]

An alternative approach was explored by Arnoldi *et al*, who reported the performance of DECT using iodine maps for the detection of

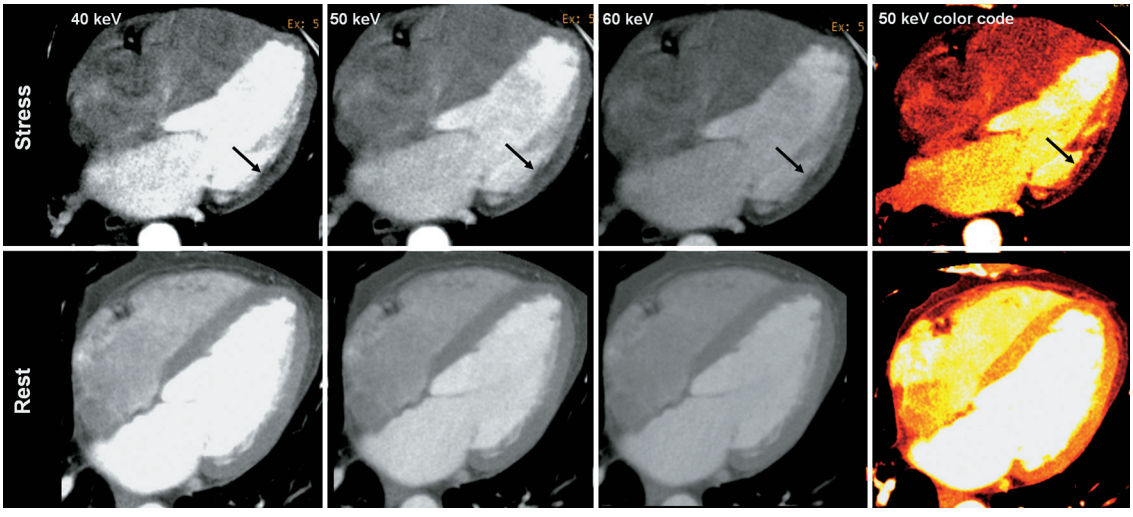

Figure 4.—Stress-rest myocardial perfusion using dual energy CT. A fully reversible perfusion defect (arrows) is observed at the left circunflex territory, more clearly depicted at low energy levels.

myocardial blood volume deficit compared to SPECT.[18] In this study, 47 patients underwent stress-rest DECT using a dual source scanner, and data was analyzed by means of: 1) high energy (140 kV); 2) low energy (80 or 100 kV); 3) merging the data (30% low and 70% high spectra); and 4) iodine maps. The authors found no significant differences between groups with regards to specificity or positive predictive value. Notwithstanding, the highest sensitivity, negative predictive value, and accuracy were achieved using iodine maps (91%, 97%, and 93%, respectively).

One of the first studies exploring the role of DECT for the reduction of BHA was published by So *et al*. In this study, that included a phantom model, projection-based DECT allowed and improved quantitative myocardial CTP compared with the conventional SECT technique, attributed to a reduction in BHA.[19]

In a very small study, Weininger *et al*. reported preliminary findings of the role of adenosine-stress dynamic real-time CTP using DECT for the assessment of patients with acute chest pain.[20] In this study, performed in a second generation dual source CT scanner, patients were randomly assigned to adenosine-stress dynamic real-time CTP (group A) or to adenosine-stress first-pass dual-energy CTP (group B). Eighty eight percent of myocardial segments were assessable in group A compared to 100% in group B, with a sensitivity of 86% and a specificity of 98% for group A; compared to of 93% and specificity of 99% for group B.

The ability of DECT to attenuate BHA using monochromatic analysis was further tested by Scheske, demonstrating a significant reduction in BHA (commonly located at the basal inferior wall) at 90 keV or higher.[10]

More recently, Meinel *et al*. reported the relative contributions of rest, stress, and delayed enhancement acquisitions for the assessment of myocardial blood supply using DECT acquired by means of second-generation dual-source CT system. Iodine maps were used for the assessment of perfusion defects, and delayed enhancement acquisition was carried out six minutes after the stress scan. The sensitivity and specificity for rest scan were 92% and 98%; and for stress-only, rest/stress, stress/delayed enhancement, and the three combined the sensitivity was 99% the specificity 97%. Using the rest/stress CTP combined evaluation, 13/29 (45%) reversible perfusion defects (identified by SPECT) were uncorrectly classified as fixed, while with the combination stress and delayed acquisition, 7% of fixed defects were misclassified as reversible.

The authors concluded suggesting that rest-stress DECT acquisition should be the protocol of choice for assessment of the myocardial blood supply in DECT, and that the addition of a delayed scan did not increase the accuracy. Furthermore, it was worrysome that almost 50% of patients with reversible defects at SPECT were classified as fixed using rest-stress DE CT, although it should be noted that SPECT is an imperfect reference image modality.[21]

An additional study by Carrascosa *et al*. evaluated CTP using DECT versus SECT in 40 patients with intermediate to high likelihood of CAD, and showed a higher diagnostic performance of DECT for the detection of perfusion defects (area under the curve 0.90 *vs*. 0.80, P=0.0004). Of note, this numbers remained unaffected when including only segments affected by BHA (area under th curve 0.90 *vs*. 0.77, P=0.007).[22]

Unlike dynamic CTP, that enables a quantitative estimation by means of myocardial time-attenuation curves and myocardial blood flow, static CTP acquisitions such as single-source kVp switching are based on myocardial signal density levels. Accordingly, is important to establish the normal values of myocardial signal density using DECT at different energy levels. This has been reported by Rodriguez-Granillo *et al*., in series of non-diabetic patients referred for CTCA with normal SPECT and with absence or mild coronary atherosclerosis. Besides, the authors found that myocardial signal density levels were similar, thus attenuating or cancelling BHA, at energy levels higher than 70 keV.[23]

Combined assessment CTCA and CTP

A number of studies evaluated the feasibility of the combined assessment, and the potential

incremental value of CTP over CTCA. In this regard, the study of Wang *et al*. was among the first reports, showing a sensitivity of 68% and 81%, and a specificity of 93% and 92% per segment and per vessel, respectively for CTP; whereas the combined evaluation of CTP plus CTCA reached a sensitivity of 90% and specificity of 86%.[24]

In another small study, Kido *et al* evaluated the potential incremental value of the combined evaluation of CTCA and adenosine-stress CTP using DECT (iodine maps) in patients referred to ICA. Importanty, only 62% of the patients could be evaluated by CTCA due to severe calcification or motion, whereas 100% were assessable by the combination of CTCA/CTP, with improved diagnostic accuracy.[25]

In the study of De Cecco *et al*. the diagnostic performance was highest for stress dual energy CTP alone (area under the curve 0.85) and the combined approach (area the curve 0.80), decreasing the false-positive rate in patients at high-risk for CAD, and outperforming the sole anatomy assessment for the detection of hemodynamically significant CAD.[26]

In keeping with this findings, Carrascosa *et al*. evaluated the incremental value of CTP over CTCA using kVp switching DECT in 25 patients with intermediate to high likelihood of CAD.

DECT images were analyzed using virtual monochromatic data across the energy spectrum. In this study, CTP using DECT demonstrated a good accuracy for the detection of reversible perfusion defects, and reported that dypiridamole stress CTP provided a significant incremental value over CTCA evaluation alone [area under the curve 0.84 *vs*. 0.70, P=0.003].

Myocardial infarct characterization

Numerous studies performed with cardiac magnetic resonance including patients with both ischemic and non-ischemic cardiomyopathies have consistently shown that the presence and extent of myocardial delayed enhancement (DE) as an independent predictor of worse prognosis. In the context of ishemic cardiomyopathy there is extensive evidence demonstrating DE as a predictor of systolic dysfunction, major adverse cardiac events, arrhitmia, and death.[27-32] Furthermore, the transmural extent of DE and the scar burden have been shown as valuable predictors of functional recovery and survival after revascularization, thus revitalizing the role of myocardial viability as a therapeutic target.[33-35]

Regardless of the underlying ethiology, the common physiopathological mechanism of DE is an expansion of the extracellular space associated to irreversible myocardial damage or intersticial fibrosis. This has been validated in animal studies not only using cardiac MR, but also using cardiac CT. Indeed, numerous studies have confirmed that the contrast kinetics of gadolinium (MR) and iodine (CT) are alike.[36-38]

DE-CT has accurately shown the ability to identify late enhancement as a correlate of scar tissue among patients with acute myocardial infarction, being this related to the extent of microvascular damage, in-hospital complications, and worse both functional recovery and clincal prognosis.[39, 40] Indeed, a recent study including 92 patients with first acute myocardial infarction who underwent percutaneous coronary intervention and iodine reinjection, suggested that the presence of an heterogeneous enhancement and a relative CT density >2.2 might predict the microvascular obstruction and left ventricular remodeling.[41]

Nevertheless, the technique suffers from a limited contrast tissue resolution compared to CMR in the stable setting. Accordingly, studies evaluating the role of DE-CT in stable patients have been mostly dissapointing, showing a high specificity but a low sensitivity (61%).[42] Indeed, recent revious study by Bettencourt *et al*. explored the diagnostic performance of DE-CT for detection of ischemic scar, and tested the potential incremental value of DE-CT over a comprehensive stress-rest CT protocol for the detection of significant CAD in symptomatic patients who underwent cardiac CT (CAC scoring, stress-CT, rest CT, DE-CT), cardiac MR, and ICA+fractional flow reserve (FFR). Coronary vessels were classified as

having flow-limiting disease if they had stenoses ≥90% (≥50% in the left main stem) or an FFR ≤0.80 in vessels >2 mm. DE-CT was performed using low dose (80 kV) imaging and prospective ECG-gated acquisitions. DE-CT identintified only 9 of the 17 ischemic scars (detected using CMR as reference standard), leading to a patient level excellent specificity (98%) yet poor sensitivity (53%). Furthermore, the authors found that adding DE-CT data did not improve the overall cardiac CT accuracy for the detection of significant CAD.[43] Furthermore, dual source CT scanners did not succeed in overcoming this limitation, that is mainly related to the relatively poor contrast between scar and normal myocardium compared to CMR, that has the ability to null the normal myocardium using specific sequences.[44] Therefore, scarred myocardium assessed using single energy DE-CT is usually shown as regions where the distinction between the myocardium and the left ventricular cavity (blood pool) is not clear, ocassionaly leading to inaccurate findings.[42]

Dual energy imaging using VMI data, given the ability to mitigate or even cancel BHAs, has shown to improve the diagnostic performance of stress-CTP.[45] In addition, the remarkably higher vascular and tissue signal density levels that can be attained by means of low energy VMI shows promise to improve the discrimination of fibrotic areas in the setting of delayed enhancement CT among stable patients (Figure 5).[5]

By virtue of the ability to achieve a substantially high tissue signal density, DE-CT using low-energy VMI shows promise to improve the discrimination between scarred and remote myocardial tissue, and (partially) overcome the limited contrast to noise ratio of single energy DE-CT compared to CMR. It is worth mentioning though, that the high signal density achieved at low energy levels is accompanied by a significant increase in image noise, although this limitation will largely be solved with the recent incorporation of iterative reconstruction algorithms for the lowest energy levels (previously only avaliable for >60 keV).

In paralell to the application in patients with ischemic cardiomyopathy, the usefulness of DE-CT using dual energy should definitively be explored among non-ischemic cardiomyopathies, including hypertrophic cardiomyopathy, myocarditis, and also as an aid to electro-anatomic mapping.[46-49] The disposal of an alternative imaging technique for scar/fibrosis assessment has potential major clinical implications, in view of the rapidly rising rates of patients with implantable devices that either preclude or seriously hamper CMR image quality, particularly taking into consideration the great growth in the number of cardiac defibrillators and and resincronizing devices.

Finally, regarding safety issues, DE-CT is associated with low radiation doses, ranging from approximately 2.2 mSv using single-source dual energy imaging to approximately 4.7 mSv using dual-source dual energy imaging.[21]

Conclusions

We have reviewed the main potential clinical applications of dual energy imaging in the cardiac field. Overall, DECT has arisen as a means to broaden the scope of patients eligible for cardiac CT towards the inclusion of higher risk patients. This might be achieved as a result

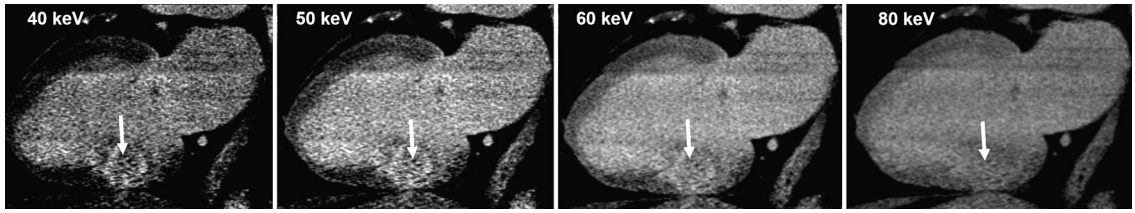

Figure 5.—Patient with previous myocardial infarction. Long vertical axis of dual energy CT acquired 8 minutes after contrast administration. Average, 7 mm multiplanar reconstructions show transmural delayed enhancement of the inferior basal wall, more clearly depicted at the lowest energy levels (arrows).

of both safety (contrast reduction) and physiopathological (myocardial perfusion and characterization) issues. Futhermore, delayed enhancement imaging using VMI data has shown auspicious preliminary data, potentially leading to an emergent role as an alternative for cardiac MR for the detection of scar/fibrosis not only in patients with previous myocardial infarction, but also in those with non-ischemic cadiomyopathies.

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Conflicts of interest.—We declare that Dr. Patricia Carrascosa is consultant of GE Healthcare.

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