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Mitya M. Barreto

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APPLICATION OF DUAL-ENERGY COMPUTED TOMOGRAPHY TO THE EVALUATION OF CORONARY ATHEROSCLEROTIC PLAQUE

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This dissertation is dedicated to my late uncle Rev. Bomventura Barreto who taught me the true meaning of education.
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APPLICATION OF DUAL-ENERGY COMPUTED TOMOGRAPHY TO THE EVALUATION OF CORONARY ATHEROSCLEROTIC PLAQUE

MITYA MARIA BARRETO

ABSTRACT

Atherosclerotic coronary artery disease is responsible for around 50% of cardiovascular deaths in USA. Early detection and characterization of coronary artery atherosclerotic plaque could help prevent cardiac events.

Computed tomography (CT) is an excellent modality for imaging calcifications and has higher spatial resolution than other common non-invasive modalities (e.g. MRI), making it more suitable for coronary plaque detection. However, attenuation-based classification of non-calcified plaques as fibrous or lipid is difficult with conventional CT, which relies on a single x-ray energy. Dual-energy CT (DECT) may provide additional attenuation data for the identification and discrimination of plaque components. The purpose of this research was to evaluate the feasibility of DECT imaging for coronary plaque characterization and further, to explore the limits of CT for non-invasive plaque analysis.

DECT techniques were applied to plaque classification using a clinical CT system. Saline perfused coronary arteries from autopsies were scanned at 80 and 140 kVp, prior to and during injection of iodinated contrast. Plaque attenuation was measured from CT images and matched to histology. Measurements were compared to assess differences among plaque types. Although calcified and non-calcified plaques could be
identified and differentiated with DECT, further characterization of non-calcified plaques was not possible. The results also demonstrated that calcified plaque and iodine could be discriminated.

The limits of x-ray based non-calcified plaque discrimination were assessed using microCT, a pre-clinical x-ray based high spatial resolution modality. Phantoms and tissues of different composition were scanned using different tube voltages (i.e., different energies) and resulting attenuation values were compared. Better vessel wall visualization and increase in tissue contrast resolution was observed with decrease in x-ray energy.

Feasibility of calcium quantification from contrast-enhanced scans by creating “virtual” non-contrast images was demonstrated. Calcium was quantified from and compared between VNC and “true” non-contrast images (120 kVp). Calcium volumes between the two were not significantly different.

DECT has potential to quantify calcium from contrast-enhanced images but is still limited in its ability to discriminate non-calcified plaques. Better spectral separation and improved resolution in clinical CT systems may allow plaque discrimination.
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CHAPTER I

INTRODUCTION

The introduction of clinical computed tomography (CT) scanners capable of cardiac imaging has improved the evaluation of several heart-related diseases. The non-invasive (except for x-ray radiation) nature of the modality, low discomfort to the patient and rapid imaging time, makes it an attractive and cost effective modality for diagnostic imaging. Coronary imaging using CT (i.e. CT angiography) is now a well-established diagnostic procedure. However, CT imaging is still limited in its ability to differentiate small, low-density tissue (e.g. atherosclerotic plaque) (1). Dual-energy CT (DECT) techniques have the potential to improve characterization of such tissue.

The goal of this work is to explore the hypothesis: Coronary atherosclerotic plaque can be characterized using dual-energy computed tomography. This hypothesis will be tested in three aims:

Specific aim 1: To characterize coronary atherosclerotic plaque using dual-energy computed tomography.
Specific aim 2: To explore the limits of clinically available x-ray based modalities for classification of atherosclerotic plaque.

Specific aim 3: To separate calcium from iodine using dual-energy computed tomography.

This dissertation is organized as background (chapters II-V), preliminary work (chapter VI) and specific aims (chapters VII-X). Chapter II includes background on the heart anatomy and coronary atherosclerosis. Chapter III of this dissertation introduces the basics of x-rays including their production and interaction with materials. Chapter IV describes current day CT technology, image reconstruction and display with special emphasis on cardiac CT and DECT. The next chapter (V) describes the different imaging modalities used to diagnose the disease followed by a review of current literature. This review includes a description of plaque characterization, calcium quantification, and DECT and microCT imaging. The problem of classifying and quantifying plaque is also described. The potential use of DECT for coronary atherosclerotic plaque characterization is explained. Also, microCT is introduced for exploring the limits of clinical CT.

Chapter VI includes details of the preliminary studies performed to establish imaging protocols for plaque classification and calcium quantification using DECT and low-density tissue characterization with microCT imaging. The experimental setup and contrast agent injection protocol are also described in this chapter.

Chapter VII describes the potential application of DECT for identification and classification of coronary atherosclerotic plaque evaluated using excised human coronary arteries (specific aim 1). The experimental methods, results and a discussion based on
these finding are included in this chapter. Outcomes of the first specific aim lead to the
development of specific aims 2 and 3. Outcomes of specific aim 1 were published in the
July 2008 issue of the Journal of Cardiovascular CT.

The limits of current day clinical CT systems (specific aim 2) are addressed in
chapter VIII. MicroCT was used to explore limitations in resolution and x-ray spectrum
of clinical CT scanners.

The third specific aim of this dissertation is the application of dual-energy CT for
quantification of calcium from contrast-enhanced images. A commercially available
software which creates virtual non-contrast images was evaluated for its ability to
quantify calcium in a phantom. The methods and results from this study have been
described in chapter IX. The possible use and limitations of this software has been
discussed. Outcomes of this work are being submitted for publication as a technical note.

Chapter X is a continuation of specific aim 3. A method for quantifying
atherosclerotic plaque from ex-vivo coronary arteries was developed. This algorithm and
its use in calcium scoring have been described in chapter X. This novel method for
quantifying calcium from contrast-enhanced images was validated against the clinical
method currently used. The advantages and disadvantages of calcium quantification using
the developed algorithm have been explained. This work has been submitted for
publication.

This dissertation concludes with a brief summary of the findings and relevance to
clinical atherosclerotic imaging using DECT.

The appendices include the program for creating VNC image written in Matlab
and the protocol for making saline.
CHAPTER II

THE HEART

2.1 Heart anatomy

The heart is a four-chambered organ whose primary function is to circulate blood throughout the body (2). It has two atria where blood is received and two ventricles through which blood is pumped out. Blood from the body returns to the right atria. It then flows to the right ventricle via tricuspid valves and is then pumped out of the right ventricle to the lungs. The lungs return oxygenated blood to the left atria. Blood then flows into the left ventricle via bicuspid (mitral) valves. The left ventricle then pumps blood to the body. The phase during which the heart muscle is contracting (to pump blood out of the ventricles) is called systole and the phase during which the heart muscle is relaxed (to allow filling of the chambers) is called diastole.

Coronary arteries provide the heart muscle with nutrients. Two main coronary arteries branch out from the aorta: right main and left main. The left main further branches into the left anterior descending and the left circumflex coronary arteries. The
coronary arteries further branch into smaller arteries and capillaries that supply blood to the heart muscle.

An electrical impulse initiates the contraction of the heart muscle (2). This electrical activity can be recorded over the cardiac cycle and is called the electrocardiograph (ECG). The ECG signal consists of a P-wave, QRS-complex, T-wave and a U-wave. The P-wave is the initial phase of the ECG signal where the electrical impulse spreads from the right atrium to the left atrium. The QRS complex indicates
depolarization (which causes contraction) of the ventricles. T-wave is caused by the repolarization of the ventricles. The time between the QRS-complex and the T-wave is called the ST-segment (ST-interval) during which the heart is relatively motion free. This time interval ranges from 80 - 120 ms. A disorder of the conducting system, which causes an irregular, or fast heart rate is called an arrhythmia. Arrhythmias are present in patients with numerous pathophysiological conditions.

![ECG signal](image_url)

Figure 2-2. ECG signal.

### 2.2 Atherosclerosis

Atherosclerosis is a complex vascular disease. Extensive research has been done to understand the mechanism of development of this disease. Once thought to be a disorder due to lipid metabolism, it is now widely accepted to be a disease caused by inflammation, yet its progression is not completely understood.

Atherosclerosis formation is due to endothelial injury (3-5). The activated endothelial cells recruit monocytes and T-cells causing a cascade of inflammatory
response in which leucocytes are activated in the media resulting in proliferation of smooth muscle cells. The monocytes adhered to the injured endothelium also recruit macrophages into the endothelium, which release more cytokines and growth factors. The activated monocytes cause oxidation of low-density lipoproteins (LDL), which are then taken up by the macrophages through their scavenger receptors to form foam cells. These foam cells are deposited in the intima initiating the development of atherosclerosis. As time progresses the lesions become more complex.

The morphology of the atherosclerotic lesion changes with time. Occlusion of the vessel lumen and calcification are observed in advanced disease (6-9). Due to the complexities involved in the stages of the disease, Stary et al (7-9) wrote a series of special reports for a standard classification of these lesions. According to this classification, there are six types of atherosclerotic lesions, namely types I to VI. Type I and type II are early lesions, type III is an intermediate lesion leading to type IV, which is called atheroma. Types IV, V and VI are considered advanced lesions or vulnerable plaques. Type V lesions are further classified into type Va, Vb and Vc. Finally type VI, is called a complicated lesion due to disruption of type IV and V. Type VI may further be subdivided. Type I and II are early lesions that cannot be visually identified. These, though found in adults, are mostly found in infants and children. Type I consists of small isolated groups of macrophage foam cells in areas of the vessel where adaptive intimal thickening has occurred. Type II may be visible to the unaided eye as yellow-colored streaks and are more distinct than type I lesions. These yellow streaks are adjacent layers of macrophage foam cells. Other cells like T-lymphocytes and mast cells can also be found in these lesions. Along with intimal thickening, an increased number of
macrophages are observed in the intima. Depending on the level of intimal thickening, type II lesions may or may not progress to type III. The progression-prone lesions are classified as type IIa and the progression-resistant lesions are type IIb. Type III are preatheroma that eventually develops into atheroma or type IV lesions. This lesion consists of extracellular lipid droplets that are either membrane bound or free that lie below the macrophage layers and foam cells. In addition to destroying the structure of the smooth muscle cells these lipid pools replace intercellular matrix proteoglycans and fibers.

The type III lesion advances to type IV with a well-defined structure. The extracellular lipids are no longer in droplets but accumulate to form what is called the lipid core. The disorganization of the intima observed in type III is now severe. The arterial wall begins to thicken externally even though no lumenal thickening takes place.

Type V are all lesions, which have a fibrous cap. A type V lesion with a lipid core is called a fibroatherma or type Va. If the lipid core is calcified it is called Vb and if the lipid core is minimal it is called Vc. Disrupted lesions are classified as type VI. Type IV and V are highly unstable plaques due the lipid pools and newly formed fibrous caps. Type VIa lesions are lesions, especially type IV and type Va, where the surface has disrupted. Type VIb are lesions in which hematoma or hemorrhage occurs due to intimal tears or rupture of the vasa. Type VIc are lesions where thrombosis has occurred.
CHAPTER III

X-RAY BASICS

3.1 Production of X-Rays

X-rays are electromagnetic radiation with wavelength 10 to $10^{-5}$ nm of which 0.1 to $10^{-2}$ nm are used for diagnostic purpose (10). X-rays are produced when fast moving electrons are suddenly decelerated losing their energy in the form of electromagnetic radiation (10, 11). Two types of x-rays produced are general or bremsstrahlung radiation and characteristic radiation.

3.1.1 Bremsstrahlung Radiation

Bremsstrahlung radiation is also known as “braking radiation” (German; *bermsen*, to brake and *Strahlung*, radiation) (10). This radiation is produced by the interaction of an electron with the nucleus of an atom (Figure 3-1). The fast moving, negatively charged electron is attracted by the positively charged nucleus. When the electron passes near the nucleus it deflects and decelerates loosing some of its energy, which is radiated in the
form of a photon. These interactions between electron and nucleus can continue until the electron looses all of its energy producing a spectrum of x-rays. The energy of the photon depends on the distance of the electron from the nucleus and increases with interactions with electrons closer to the nucleus. If the electron collides head on with a nucleus, the electron looses all of its energy to form a single photon with highest energy in the spectrum.

Figure 3-1. Illustration of general radiation. Maximum x-ray energy is radiated when the incident electron collides with the nucleus. The energy of x-rays decreases as the distance between the incident electron and nucleus increases. Adapted from Bushberg et al (10).
Figure 3-2. Bremsstrahlung spectrum showing attenuation differences in the filter and unfiltered beams.

Figure 3-3. Illustration of characteristic radiation. Electron is ejected from the K-shell resulting in x-rays characteristic of the k-shell. Adapted from Bushberg et al (10)
3.1.2 Characteristic Radiation

Characteristic radiation occurs when a moving electron interacts with inner shell electrons in an atom (Figure 3-3) (10, 11). Each shell is denoted letters K, L, M, N … with K being the innermost shell. The binding energy of each shell is the energy required to free an electron from that shell. If the electron has more energy than the binding energy of a shell, the shell electron is freed ionizing the atom. An electron from the outer shell of the ionized atom will jump to the vacant shell releasing energy in the form of a photon. The energy of the emitted photon equals the difference in binding energies ($E_b$) of the two shells (Figure 3-4):

$$E_{\text{Characteristic}} = E_{b \text{ vacant shell}} - E_{b \text{ transition shell}} \quad \text{... Equation 1}$$

Figure 3-4. Illustration of x-ray spectra with filtered bremsstrahlung and characteristic radiation. Characteristic radiation from adjacent shells ($K_{\alpha}$) has higher energy than characteristic radiation from non-adjacent shells ($K_{\beta}$).
The energy difference between two shells and the binding energy of each shell are also unique to each element (Equation 1). Therefore, this radiation is “characteristic” of the material and its shell. Therefore, x-rays produced by characteristic radiation have discrete energies.

### 3.2 X-ray Tube

X-rays are produced in a vacuum tube enclosing two electrodes: an electron source or the cathode and the target or anode (Figure 3-5). An external voltage source is applied across the electrodes to accelerate the electrons from the cathode to the anode (10, 11).

![Figure 3-5. Schematic of x-ray tube.](image)

#### 3.2.1 Cathode

The cathode or the negative electrode consists of a helical filament made of tungsten wire. The filament is connected to an electrical source, which produces an
electric current through the wire. This current heats the filament thus liberating electrons. The filament current controls the number of electrons liberated. The stream of liberated electrons flowing from the cathode to the anode is called the tube current and is traditionally, stated in milliamperes (mA).

3.2.2 Anode

The anode is the positive terminal of the x-ray tube, the target electrode. The anode is made of tungsten or some alloy of tungsten, which has a high atomic number and high melting point. In CT systems a continuously rotating anode disk is used to accommodate the high heat produced by the incident electron stream over scan time. The size of the anode area exposed is called the focal spot of the x-ray beam. Often x-ray tubes offer two foci: large (used for scanning large volumes due to higher power required) and small (used for thin slices and high resolution).

3.3 Interaction of radiation with matter

As x-rays pass through a material, photons from the beam are removed or attenuated. Attenuation of x-rays occurs through absorption and scatter. These interactions with matter can occur in five different ways: coherent scattering, photoelectric effect, Compton scattering, pair production and photodisintegration (10, 11). Of these only Compton scattering and photoelectric effect are significant in diagnostic radiology.
3.3.1 Compton scattering

Compton scattering occurs when an incident photon collides with the outer shell (free or valance) electron freeing it from its orbit (Figure 3-6). The photon looses some of its energy to the freed electron and is deflected to a new direction. The amount of energy lost depends on the angle of deflection and the energy of the incident photon; with increased energy of the incident photon, the angle of deflection decreases and the energy transferred to the scattered electron is increased. The deflected photon is still left with enough energy to penetrate through an object to the detectors increasing image noise.

The probability of Compton scatter increases as the density of the material increases. The probability of Compton scatter also increases as the energy of the incident photon increases. Further, as the energy of photons increases their penetrability increases resulting in low attenuation as most photons are transmitted through matter. Therefore, contrast between materials is low with the occurrence of Compton scatter.
3.3.2 Photoelectric effect

Photoelectric absorption occurs when the energy of the incident electron is greater than the energy of the interacting electron (Figure 3-7). Some energy of the incident electron is utilized to overcome the binding energy of the interacting electron, releasing it from the shell. The remaining energy is transferred to the interacting electron. As a by product of this interaction, electrons from higher energy shells jump to the lower energy shell trying to fill the vacancy and in doing so, emit radiation (Figure 3-7) (11). This cascade of electrons from higher energy shells continues until all lower energy shell electron vacancies are filled. Therefore, dose to patient is high due to radiation from the cascading electrons, which is absorbed by the surrounding tissue. However, this interaction produces less noise in the images due to low scatter.
The probability of photoelectric effect increases with the atomic number of the material \((Z)\) and decreases with increase in x-ray energy \((E)\):

\[
Photoelectric\,\,\,Effect \propto \left(\frac{Z^3}{E^3}\right) \ldots \text{Equation 2}
\]

Because photoelectric effect increases with the third power of the atomic number, a slight change in the atomic number of tissue magnifies attenuation differences in the tissue providing more contrast between tissue types. With increasing x-ray energy, however, the occurrence of photoelectric effect decreases, thereby reducing the amplification of attenuation differences in tissue and lowering tissue contrast.

Figure 3-7. Illustration of Photoelectric effect. The incident electron (wavelength \(\lambda_1\)) interacts with the k-shell electron removing it from the shell. Electrons from outer shell jump to fill up the vacant space emitting radiation characteristic of each shell (wavelength \(\lambda_2, \lambda_3\)). Adapted from Bushberg et al (10).
In order for an electron to be removed from its shell, the energy of the incident electron has to be higher than the binding energy of the electron shell. If the energy of the incident electron is slightly lower than the binding energy of the shell no interaction occurs. Therefore, the incident electron is transmitted through the material without interactions. However, if the energy of the incident electron slightly exceeds the binding energy of the electron shell, the energy of the incident electron is rapidly utilized to eject the electron from the shell. The attenuation of x-rays sharply increases at the absorption edge of a material. This energy, called the absorption edge, at which the sharp discontinuity in absorption occurs is unique to each element and its shell. An absorption edge at the k-shell is called k-edge and so on.

Soft tissue consists of elements with low atomic numbers. Therefore, the probability of photoelectric interactions is low, reducing contrast in soft tissue. However, low energy photons can be used to magnify the difference in tissue at their absorption edges. In case of higher atomic number elements commonly encountered in medical imaging such as calcium, iodine and barium, photoelectric absorption is important as these material emit radiation characteristic to their k-edge in the diagnostic x-ray energy range. Therefore, two separate x-ray energies can be used to discriminate between materials by taking advantage of their unique absorption characteristics.

### 3.3.3 Linear attenuation

The attenuation of x-rays through a material is measured in terms of its linear attenuation coefficient ($\mu$). The linear attenuation coefficient of a material is defined as the fraction of photons removed from the x-ray beam per unit thickness of the material. The amount of attenuation of photons depends on the atomic number, density and
electron density of the material and also, the energy of the incident x-ray photon. The number of x-ray photons removed from the x-ray beam will increase with higher density of electrons in its path. Therefore, the linear attenuation coefficient of a material depends on its physical state (i.e. gas, liquid, solid). The amount of x-ray attenuation also depends on the energy of the incident beam, which makes the linear attenuation coefficient dependent on the x-ray energy. The linear attenuation coefficient of a material decreases with increase in the x-ray energy. However, at the absorption edge of a material this trend changes. In order for an electron to be removed from its shell, the energy of the incident electron has to be higher than the binding energy of the electron shell. If the energy of the incident electron is slightly lower than the binding energy of the shell no interaction occurs. Therefore, the incident electron is transmitted through the material without interactions. However, if the energy of the incident electron slightly exceeds the binding energy of the electron shell, the energy of the incident electron is rapidly utilized to eject the electron from the shell. The attenuation of x-rays sharply increases at the absorption edge of a material.

The number of photons (N) that are transmitted through a material of thickness x for a monoenergetic x-ray beam of photons (N_o) can be measured by

\[ N = N_o e^{-\mu x} \quad \text{… Equation 3} \]

This equation describes the number of photons (or intensity) in the x-ray beam that are attenuated and does not affect the energy (or quality) of the x-ray beam. The amount of attenuation increases exponentially with the linear attenuation coefficient and the thickness of the material.
CHAPTER IV

COMPUTED TOMOGRAPHY BASICS

4.1 Introduction

In a modern CT system, the x-ray source and detector array are mounted opposite to each other on a circular gantry, rotate around the patient bed (Figure 4-1). CT scanners have evolved from first generation pencil-beam rotate/translate single detector row systems to modern cone beam, multi-detector row systems (10-13). It is now possible to continuously rotate the x-ray tube in a single direction without the need for untwisting the power chord allowing spiral acquisition of data. Before reaching the detectors, the x-ray beam passes through several filters. These filters are used to improve the quality of the beam by removing lower energy photons, geometrically shape the beam and reduce scatter from reaching the detectors. Further, multi-row detector arrays allow acquisition of data over a large x-ray cone beam. These innovations have reduced scan times significantly improving CT image quality and patient comfort. The speed with which the gantry rotates relates directly to the image acquisition time and exposure. Also, in cardiac applications the temporal resolution is defined by the gantry rotation speed.
The following subsections will focus on the technical innovations of the CT scanner used in this research.

Figure 4-1. Illustration of a CT system.

4.2 Multi-detector row arrays

Multi-detector row array CT scanners for cardiac imaging were introduced in 1998 (13) although the technology itself existed since the early 1980’s. The number of slices that can be acquired in a single scan depends on the arrangement of the detectors. The width of the detector at the isocenter of the scanner defines the thinnest slice that can be acquired. Thicker slices can be acquired by combining multiple detectors during acquisition (binning) or combining the signal over multiple detectors during reconstruction. An isotropically (a.k.a. fixed array detector) designed detector array uses
detector elements of the same size while an anisotropically (a.k.a. adaptive array detector) designed detector array uses thinner detectors at the center and wider detectors at the edges (14). In an anisotropic system only the central detectors are used for acquiring thinnest slices; to acquire thicker slices multiple detector are combined. The scanner used in this work has an anisotropic detector array (Figure 4-2). Each detector column consists of forty detector elements. Each detector row consists of approximately 800 detector elements along the detector arc. Thirty-two central most detectors are the thinnest (0.6 mm) and the outer detectors (four on each side) are twice as wide (1.2 mm). Therefore, only the central most detectors are engaged for acquisition of the thinnest slices (32 x 0.6 mm). The detectors are combined to produce thicker slices. For example, for a slice thickness of 1.2 mm the central 32 detectors are paired to form 16 slices of 1.2 mm in additional to the 8 outer 1.2 mm detectors resulting in 24 slices of 1.2 mm per rotation (15).

Figure 4-2. Schematic of detector arrays representing isotropic (top) and anisotropic (bottom) detector designs.
4.3 Dual Source

The scanner used in this study (Siemens Definition, Siemens Healthcare, Erlangen, Germany) is a dual source (two x-ray tube and detector arrays) scanner system (16). Two tubes are mounted on the gantry orthogonally to each other. Also, two detector arrays are mounted opposite to each of the tubes (Figure 4-3). The x-ray tubes can be operated both at the same tube voltage or independently at different tube voltages. Also, the tube current across each tube can be controlled independently. The minimum gantry rotation time is 330 ms, which allows up to 83 ms temporal resolution in a cardiac mode (explained in following sections).

Figure 4-3. Illustration of a dual source CT scanner.
4.4 Data Acquisition

4.4.1 Data Acquisition modes

Modern CT scanner can acquire images in two modes; sequential (a.k.a. axial, step and shoot) or spiral (a.k.a. helical).

Sequential

In a sequential mode of scanning, 360° (or 180° for partial scans) of projection data is acquired while the table is stationary. The table is then moved in increments of the collimated detector width to the next slice position (hence, step and shoot). This process is repeated until the desired anatomy is covered. Since the x-ray tube is on only for the time that data is being acquired and off when the table is moved, this method offers the advantage of radiation dose savings.

In cardiac imaging the scan acquisition is synchronized to the cardiac cycle. The cardiac phase for data acquisition and, therefore, image reconstruction is selected prior to scanning. The scan is triggered by the R-peak of the ECG signal and data are acquired only during the pre-selected phase of the cardiac cycle. However, in case of arrythmia or irregular heart-beats, the length of the RR-interval signal changes. Therefore, this mode of scanning is more susceptible to motion artifacts with irregular heart rates (12).

Spiral

With the availability of slip-ring technology, a spiral or helical mode of acquisition became possible (13). In spiral mode of acquisition the x-ray tube is continuously rotated around the patient bed while the bed is moved through the beam at a
constant speed. The resultant data are acquired in a spiral pattern; amount of overlap in data depend on the pitch (discussed later in this chapter).

An advantage of spiral acquisition is the significant improvement in scan speed. This is critical for cardiac imaging as it reduces the breath hold duration, thereby reducing the occurrence of respiration motion artifacts. Also, as data collection is continuous and has no gaps, this mode of acquisition allows image reconstruction over multiple desired phases of the cardiac cycle. Radiation dose however increases, due to the continuous x-ray exposure (12).

4.4.2 Acquisition parameters

Figure 4-4. A single view created by rays projected (projections) on to a row of detectors.
Prior to data acquisition, the parameters that need to be selected are tube voltage, tube current, pitch (for spiral), gantry rotation time and detector width collimation.

**Tube voltage**

Tube voltage is the potential difference applied across the x-ray tube to accelerate the electrons from the cathode (filament) to the anode. The energy of the produced x-rays is proportional to the applied tube voltage. In the case of diagnostic imaging the term tube voltage is used synonymously to x-ray energy and is indicated in terms of kilovolts (kV). X-ray tubes used in current day CT scanners produce polychromatic x-rays. In such a case, the tube voltage denotes the maximum possible x-ray energy that will be produced and is measured in peak kilovolts (kVp). The tube voltage defines the quality of x-rays. Increasing the tube voltage increases the penetrability of the x-rays. This increases the number of photon reaching the detector therefore increase the SNR. However, because photoelectric interactions decrease with an increase in tube voltage, tissue contrast is diminished. Also, as the energy of the x-ray photons increases the radiation dose increases proportional to the square of the tube voltage \((\text{dose} \propto (\text{peak tube voltage})^2)\) (12).

**Tube current**

The number of photons accelerated from the cathode to the anode is called the tube current and is measured in terms of milliAmperes (mA). Hence, the tube current is a measure of x-ray quantity. The number of x-rays produced is directly proportional to the tube current. Increasing the tube current allows for more interaction with the tissue, therefore improving the SNR. However, increasing the tube current increases the radiation dose.
Pitch

Pitch (p) is defined as the ratio of the table increment or table feed (d) to the nominal beam width (17).

\[ p = \frac{d}{M \cdot S} \] … Equation 4

The nominal beam width is the product of the number rows (M) and row thickness (S). In the case of a single row system this is simply the distance the table moves per row. Pitch is a dimensionless parameter; a pitch of > 1 means there is no overlap of the acquired data along the direction of patient movement, while a pitch of less than 1 indicates overlap in data acquisition. This parameter plays an important role in the quality of acquired data (noise) and patient dose.

For cardiac imaging, the pitch has to be adjusted to the patient heart rate. To avoid cardiac motion artifacts, data is acquired only during the relatively stationary period (indicated by ST-segment of the ECG signal) of the cardiac cycle. To avoid discontinuities in the acquired data a higher temporal resolution will require a lower pitch. For a multi-row detector system of gantry rotation time \( T_{\text{rot}} \) and R-R interval of the ECG signal (\( T_{RR} \)) (18); The upper limit on pitch can be completed an follows;

\[ \text{pitch} \leq \frac{(M - 1)T_{\text{rot}}}{M \times T_{RR}} \] …Equation 5
4.5 Reconstruction parameters

4.5.1 Collimated detector-row width

The collimated detector-row width is thickness at the isocenter of the scanner in the z-dimension (longitudinal) over which a single view of data (in the x-y direction) is gathered (19). The minimum achievable thickness of an image is determined by the physical width of the detector element. Also, clinical CT scanners allow reconstruction of thicker slices from data acquired with a thinner detector width collimation. Although thinner slices improve z-resolution, image noise increases due to less photons reaching the detector (i.e low SNR). Increasing the tube current can offset losses in SNR, which results in a radiation dose penalty. Therefore, in instances where high z-resolution is not a priority, data from multiple detectors can be combined or binned together to produce thicker slices improving SNR without increasing dose.

4.5.2 Scan Field-of-View

The scan field-of-view (sFOV) defines the largest planar (x-y) dimensions that can be scanned. The reconstructed (rFOV) is the portion of the scan sFOV chosen for display (sFOV ≥ rFOV). The recon FOV is a square area, which is divided into a matrix of 512 x 512 pixels in a typical CT image. Therefore, the reconstructed FOV defines the pixel resolution in each image by the equation that pixel size (mm) = RFOV/512 mm.

4.6 Z-flying focus principle

The z-flying focus principle describes the electromagnetic deflection of the electron beam in the x-ray tube using electromagnetic deflection to improve sampling in
the z-direction (15, 16). The focal spot is wobbled such that the x-ray beam is shifted by exactly half the collimated row thickness at the isocenter (Figure 4-5). The CT scanner used in this study uses an x-ray tube with z-flying focus principal to produce a maximum of 64-slices per rotation. Thirty-two detectors are available in the array at the thinnest row collimation (D = 0.6 mm). As the x-ray beam moves at half the collimator width (0.3 mm) at the isocenter each detector “sees” two views of 0.6 mm width. Hence, two interleaved readings produce 0.6 mm thick views with 0.3 mm overlap fulfilling Nyquist sampling theorem (sampling rate should equal at least twice the row width).

Figure 4-5. Z-flying focus principal (15, 20).
4.7 Image Reconstruction

The linear attenuation coefficient (μ) from each projection is calculated as the natural logarithm of the incident or reference x-ray signal (I₀) to the recorded signal (I₁) (10, 11).

\[ \ln(I₀/I₁) = μx \] … Equation 6

The linear attenuation coefficient μ is the sum of attenuation coefficients along the ray path (x) (equation 6). Therefore, if the path of the incident x-ray is broken down to small length increments of Δx then the linear attenuation coefficient of the voxels in Δt is

\[ μx = (μ₁ + μ₂ + … + μ₃) Δx \] … Equation 7

Using data from every projection through a particular voxel, the linear attenuation coefficient for that voxel can be approximated. Several algorithms are used for reconstruction: interpolation/iterative and filtered back projection.

The iterative reconstruction algorithm uses a first “guess” for the attenuation coefficient. The error in the guessed and actual value is reduced in successive iterations, interpolating data from neighboring projections (13). Due to the iterative nature of this algorithm it is computationally expensive. However, it provides higher accuracy in the attenuation values as compared to other reconstruction algorithms (12).

A backprojection algorithm is a mathematical approach that uses the attenuation coefficients, the angle of the x-ray and position of detector to fill a line in the image matrix corresponding to the image path. However, objects appear blurred in the images due to assumptions of the rays’ projection. To reduce the blurring, data is convolved with
a filter. This modified backprojection algorithm is called filtered backprojection and is the most commonly used reconstruction algorithm in clinical CT systems today (10, 11).

Cardiac imaging uses partial scan reconstruction algorithms that require only 180° (instead of 360°) of projection data. This is possible since projections from one direction contain the same attenuation information as projections from exactly the opposite direction (i.e., projections 180° apart) (13).

4.7.1 Reconstruction kernels/filters

The type of kernel or filter used to reconstruct an image depends on the features of the image that need to be enhanced (10, 11). In scans where high image contrast is of more importance than spatial resolution, a kernel with more roll off at high frequencies is used. As a consequence of the high frequency roll off, noise is reduced in the image improving image contrast. However, edges, which are high frequency components, are lost. These kernels are called smooth filters or also, soft tissue filters in clinical applications. Conversely, in images where high attenuating materials are present, such as bone and stents, it may be necessary to maintain sharper edges. Sharp kernels used in these cases, therefore, have a lower high frequency roll off. This comes at the cost of increased noise in the image and hence, low contrast resolution.

4.7.2 Reconstructed Slice Thickness

The thinnest slice that can be reconstructed is determined by the collimated detector row width. The slice thickness defines the maximum resolution of the image in the z-direction. However, if it is necessary to reduce overall image noise reconstructing thicker images is possible (14).
4.7.3 CT number and Hounsfield Unit

The reconstructed image is comprised of intensity values representing the attenuation coefficient of the material. These values are strongly dependent on the materials being scanned and the x-ray energy at which they are scanned. So that the intensity values have a common reference, the image data is calibrated with respect to water. The CT number is defined such that at all x-ray energies the intensity of water is zero. The CT number of a material with attenuation coefficient \( \mu \) is defined as:

\[
CTnumber = \frac{\mu - \mu_{water}}{\mu_{water}} \times 1000 \quad \text{… Equation 8}
\]

The unit for CT number when magnified by 1000 (equation 8) is Hounsfield units (HU) in honor of Godfrey Hounsfield (10, 11).

Any material with density and, hence, intensity less than water will have a negative value and materials with density higher than water will have a positive value. Air, which has a density of 0.001293 g/cm\(^3\) is very much lower than water and therefore yields a CT number of -1000 HU. The CT number of the pixels increases as attenuation of a material increases with the most attenuating material represented as high CT number. In most clinical systems, the range of CT number is limited by the number of bits used to represent the data. For example, in a 12 bit system the CT numbers range from -1024 to 3072 (2\(^{12}\) values). For medical applications this range is sufficient as bone (calcium) is the highest attenuating material found naturally in the body. Any material (stents, metallic implants, etc) that may attenuate more will require a larger range.
4.7.4 Contrast Resolution

Contrast resolution is the ability of a system to distinguish two low-density materials (10, 11). Low contrast resolution is measured in terms of the contrast-to-noise ratio (CNR), the difference in attenuation between two materials divided by the noise in the image. This measure depends not only on the noise in the image and but also on the spatial resolution. More homogeneity in the image background (i.e. less noise) improves the distinction between two materials of similar densities. Further, small objects will have better contrast if the spatial resolution is high enough to resolve the objects. Superior low contrast resolution is important for the discrimination of plaque since, non-calcified plaque components have similar densities. Therefore, image noise should be kept at a minimum.

4.7.5 Windowing and leveling

Typically, in diagnostic systems the CT number is 12-bit with values ranging from -1024 to 3072 HU. A digital display can resolve only 256 levels of gray and the human eye can perceive even fewer levels. To maximize the visible contrast in the tissue of interest, a sub range of available CT numbers are displayed; the window width, w, above which all pixels are white and below which all pixels are black. The mid point in the window width is defined as the center or level and this CT number is defined as the mid-level gray. This method of selecting a range of CT numbers to display on the fly is called windowing and the CT number at which this window is centered is called window level or center (13).
4.8 Dual-energy CT

In the diagnostic range, x-rays primarily interact with matter through Compton scattering and photoelectric interactions. The linear attenuation coefficient can be expressed as a combination of the photoelectric absorption $\mu_p$ and Compton scatter $\mu_c$.

$$\mu = \mu_p + \mu_c$$

$$\mu_p = k_p \rho Z^s / E^3 \quad \text{… Equation 9}$$

$$\mu_c = N_a Z A f_{KN}(E)$$

Where $k_p$ is a constant, $f_{KN}$ the Klein-Nishina function, $N_a$ is the Avogadro’s constant and $A$ is the atomic weight. The following equations express the dominance of photoelectric absorption increases directly as the atomic number of the material ($Z$) increases. Photoelectric interactions rapidly decrease with increase in the x-ray energy ($E$). Therefore, Compton scatter becomes the predominant interaction at high x-ray energies. Compton scatter per unit volume increases with increase in density of the material ($\rho$) (21). Hence, a change in x-ray energy results in different attenuation in the same material. This principal has been explored for its use in identification of matter and has, subsequently, been used in medical applications for tissue characterization.

A popular application of dual-energy x-rays is subtraction of bone (calcium) or contrast agent (iodine) in images. Also, as diagnostic x-ray energies commonly available on clinical CT systems can easily identify calcium, dual-energy CT is used for measurement of bone mineral density (22) and identification of nodules in lungs/chest and liver (23) as well as renal stones (24).

Dual-energy acquisition can be done either by scanning at two different x-ray energies (12, 16) or by using energy selective filters (25, 26). Currently available DECT
systems use dual-source operated simultaneously at two different tube voltages (16) or a signal source system that rapidly switches the tube voltages between high and low during (12). Dual-energy data can also be acquired from a single polychromatic source by using energy selective detectors. The energy can be binned into several separate spectra (27, 28) or two separate energies using a dual-layer detector (25). Also, post-processing techniques can be used to separate the Compton scattering component and photoelectric absorption from the polychromatic x-ray source.

4.9 Cardiac CT

Cardiac imaging was made possible with the capability to synchronize the ECG signal to data acquisition or reconstruction. Improvements in gantry rotation speed, half-scan reconstruction algorithms and multisegment reconstruction algorithms resulted in temporal resolution suitable for cardiac imaging (13, 18, 29, 30). Cardiac imaging has also benefitted from the increased z-coverage and z-spatial resolution available with newer systems.

4.9.1 ECG referencing

The heart is in continuous motion. This makes it difficult to reconstruct blur free images. During every cardiac cycle there is a short diastolic time window when the heart is relatively free of motion. Projections obtained during this time period by synchronizing data acquisition or image reconstruction to the ECG signal (i.e. ECG referencing) can, therefore, be used to reconstruct images relatively free of cardiac motion artifacts.

35
Retrospective ECG gating allows the user to reconstruct during any phase of the cardiac cycle whereas prospective ECG-triggering requires selection of the desired cardiac phase prior to scanning (29).

4.9.2 Tube current modulation

In order to lower dose to the patient, x-ray tube current can be modulated according to the anatomy of the patient, or in the case of cardiac imaging according to the ECG signal.

Anatomy based current modulation adapts the tube current to the thickness of the patient. This method lowers the current through the thinner dimensions of the body and increases the current through the thicker dimensions. Similar noise levels are achieved with and without anatomic based tube current modulation while the overall dose to the patient decreases significantly (12, 31).

ECG-based tube current modulation can be used prospectively in helical mode of acquisition (12). In retrospectively triggered-helical imaging, the current is lowered outside the phase of interest while it is increased during the phase of interest. Since the tube is on throughout the cardiac cycle, data is available although with reduced signal, for reconstruction.
4.10 CT Artifacts

4.10.1 Partial volume averaging

When a highly attenuating object partially covers a voxel, the intensity of the voxel appears higher than its true value. This increases the overall appearance of the object’s size (Figure 4-6). This is called partial volume averaging or “blooming” artifact and is prominent with dense materials like calcium, iodine and metal implants (32, 33). Reconstructing thinner images, which results in higher z-resolution or smaller voxel size, decreases the artifact. Also, acquiring images at higher x-ray energy decreases the “extent” of the artifact due to improved x-ray penetration and reduced intensity of dense objects.

Figure 4-6. Partial volume averaging (blue arrow) and Beam hardening (red arrow) artifacts.

4.10.2 Beam hardening artifacts

The x-ray sources used in CT scanners produce a polychromatic beam of x-rays. As a beam of x-rays enters the body, the lower energy photons are preferentially
absorbed by the body causing the beam to “harden”. Due to the loss of low energy photons, the mean x-ray energy exiting the body is significantly higher than the mean x-ray energy entering the body. This appears in the reconstructed images as streaks or dark areas near dense tissue (Figure 4-6) (32). Taking into account the density of tissue, projection of the beam and the energy of the beam itself, it is possible to mathematically correct for beam hardening in the reconstructed images (34).

4.10.3 Motion artifacts

Motion artifacts occur as a result of gross patient motion, breathing motion or cardiac motion during data acquisition causing blurring in the reconstructed images (32). This artifact cannot be corrected, as the motion is unpredictable. Respiratory motion artifacts are visible in sagittal and coronal images as stair steps and are minimized with breath holding. In cardiac imaging, heart motion is an additional cause of motion artifacts, making diagnosis more difficult (31). Cardiac motion artifact is reduced by synchronizing the scan acquisition or reconstruction to the ECG signal. Images can then be confined to the relatively stable window of the cardiac cycle (i.e. diastole).
4.10.4 Noise

Noise in reconstructed images arises from two sources; quantum noise and electronic noise (10-12). Quantum noise is scatter caused through the interactions of photons with the scanned materials. In current day clinical scanners most of the image noise is due to the quality and quantity of the detected signal ($I_0/I$). Image noise is measured as the standard deviation ($\sigma$) of pixel intensity values from their mean in a selected region of interest, measured using a water phantom.

$$\sigma = f_A \sqrt{\frac{I_0/I}{\varepsilon QS}} \quad \text{… Equation 10}$$

Noise in an image ($\sigma$) is inversely proportional to the square root of tube current-time product ($Q$) and slice thickness ($S$). Also, with higher attenuating objects the $I_0/I$ will increase noise in the images (13). $\varepsilon$ is the system efficiency. The reconstruction
kernel, accounted for in $f_A$, also affects noise. Image noise will increase with sharper kernels.
CHAPTER V

BACKGROUND AND LITERATURE

5.1 Introduction to Imaging Techniques

Coronary angiography is well established for the identification of luminal stenosis but cannot define details of plaque composition. Patient risk is not only dependent on the quantity of disease but also the progression of the disease. Hence, identifying details of the plaque characteristics is important.

Numerous techniques have been investigated, developed and applied to atherosclerotic plaque imaging. Some imaging techniques used include intravascular ultrasound (IVUS), magnetic resonance imaging (MRI), high resolution MRI, MDCT, optical coherence tomography (OCT) and high resolution CT or microCT. Imaging with minimally invasive modalities (IVUS and OCT) has defined the role of the vessel wall plaque and in particular plaque burden and the emerging role of plaque composition (35). Minimally invasive techniques typically have higher spatial resolution and also allow real-time visualization of the atherosclerotic lesion. However, these modalities are used only with planned interventions and cannot be justified for use in early diagnosis as they
involve considerable risks to patients. An advantage of non-invasive modalities is they involve minimal patient risk and hence, can be used for early diagnosis and detection of disease.

Among non-invasive modalities, MDCT is an excellent modality for imaging calcifications, MRI however is superior for imaging soft tissue. Clinical state-of-the-art MDCT scanners have better spatial resolution compared to MRI scanners. CT also offers the advantage of shorter breath-hold time, shorter examination time and lower medical cost. Furthermore, using dual-energy CT may improve soft tissue discrimination by exploiting attenuation differences as a function of x-ray energy. However, CT imaging exposes the patient to ionizing radiation.

5.2 Multislice Computed Tomography in classification of Atherosclerosis

EBCT has been used as a near gold standard modality for noninvasive coronary imaging. To view the coronary arteries without motion artifact a temporal resolution < 50 ms is needed (36). EBCT has a high temporal resolution of 50 – 100 ms, making it an attractive modality for the purpose of visualizing coronary arteries. However, it is limited in its x-ray power, which consequently limits the CNR. This has been overcome with the advent of MDCT, which offers a variable tube voltage and a wide range of tube current selections due to its higher tube power. MDCT also offers better spatial resolution, both in-plane (x-y) and through-plane (z), while reducing overall image noise. This improvement in CNR with MDCT is at the cost of increased radiation dose (37, 38).
Since the introduction of MDCT, several studies have attempted to classify coronary atherosclerosis non-invasively in phantoms (39), ex-vivo (40-45) and in-vivo both in animals (46) and humans (1, 47-57). Ex-vivo studies allow comparison to histology, the gold standard for plaque classification. Hence, plaque classification by a new imaging technique can be evaluated at a higher accuracy ex-vivo. A drawback of ex-vivo studies is the absence of motion artifact resulting from cardiac and respiratory motion that is seen frequently in in-vivo MDCT scanning of the coronary arteries. This limitation can be addressed to some extent by simulating cardiac motion ex-vivo.

In their study to characterize atherosclerotic plaque, Becker et al (40) injected coronary arteries of 11 excised human hearts, with a mixture of methylcellulose and CT contrast media. Scans were performed with a 4-slice, 500 ms rotation scanner at a tube voltage of 120 kVp, tube current of 80 mA and collimation of 2 x 0.4 mm. Data were reconstructed with a slice thickness of 0.6 mm at 0.6 mm increments using a medium smooth filter. Plaques were classified as completely calcified, mixed or non-calcified. After comparing the CTA findings with histology, non-calcified plaques were found to have Hounsfield values of 76±35 HU with predominantly lipid-rich plaque having values of 47±9 HU and predominantly fibrous-rich at 104±28 HU. These values are in agreement with those reported in other studies (Table 5-i).

Even though significant differences have been found in the mean attenuation of non-calcified plaque components, there is considerable overlap in the HU values (1). This overlap in attenuation could be due to the composition of non-calcified plaque, due to similarities in density and composition in lipidic and fibrous plaque types. Hence, the potential use of CT values at a single x-ray energy for plaque characterization poses a
challenge. Moreover, the HU values reported may not indicate the true attenuation of plaque as some studies have observed enhancement of plaque due to the presence of contrast agent in coronary arteries ex-vivo (43, 44, 58). Cademartiri et al (43) reported an increase in plaque attenuation with an increase in concentration of contrast in the coronary lumen. Halliburton et al (44) studied plaque enhancement by pressure perfusing human coronary arteries ex-vivo and comparing plaque attenuation before, during (peak attenuation) and after introduction of contrast in the vessels. Significant differences were observed for non-calcified and densely-calcified plaques between contrast-enhanced and non-contrast images. The reason for this phenomenon is not known but could be due to diffusion across the vessel wall, uptake of contrast agent through vasa vasorum present in the plaque region or interpolation of data in the reconstructed image.

In their attempt to evaluate the accuracy of MSCT in classifying plaque, Leber et al performed in-vivo studies using a 16-slice MDCT (53) and a 64-slice MDCT (54) in comparison to IVUS. In the 16-slice study (53), a collimated detector width of 12 x 0.75 mm was used. Patients with heart rates that did not fall below 65 bpm, even after administering beta-blockers, were excluded from the study. Results showed that MDCT had a sensitivity of ~78% for non-calcified and ~95% for calcified plaque. The overall specificity was ~92%. MDCT was feasible in 80% of consecutively enrolled patients. 15% of the vessels could not be evaluated due to poor image quality caused by cardiac motion artifacts. Using a 64-slice scanner (54), the overall sensitivity to detect plaque was improved. The detector width collimation used was 32 x 0.6 mm; the x-ray tube employed a wobbling beam that produced two readings per detector resulting in 64-slices per rotation. The results showed a sensitivity of 83% for non-calcified plaque and 95%
for calcified plaques. The overall specificity was 94%. This improvement compared to the previous 16-slice study could be due to the higher spatial and temporal resolution of the 64-slice scanner, 0.4 mm and 160 ms, respectively. None of the patients were excluded due to high heart rates. In cases where the heart rate could not be reduced below 65 bpm, a two-segment reconstruction algorithm was used to effectively increase temporal resolution up to 83 ms, depending on patient heart rate. However, in both studies, measured volumes of calcified lesions were overestimated. This is likely attributable in large part to partial volume averaging of calcium and contrast agent, due to the still limited spatial resolution of the CT scanner. Also, IVUS (the reference standard) has a lower ability to quantify calcifications due to the shadow overcasting tissue deeper in the vessel wall (59). Hence, comparisons of calcium volumes measured with MDCT could appear further inflated by comparison. However, non-calcified plaque volumes were underestimated as compared to IVUS. This may be due to low CNR and limited spatial resolution of the CT system.

Table 5-i. Plaque density measurements from ex-vivo multidetector computer Tomography studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of plaques (n)</th>
<th>Predominantly Lipid-rich</th>
<th>Predominantly Fibrous or mixed</th>
<th>Predominantly Calcified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becker (40)</td>
<td>39</td>
<td>47±9</td>
<td>104±28</td>
<td></td>
</tr>
<tr>
<td>Nikolaou (41)</td>
<td>21</td>
<td>47±13</td>
<td>87±29</td>
<td></td>
</tr>
<tr>
<td>Schroeder (45)</td>
<td>17</td>
<td>42±22</td>
<td>71±21</td>
<td>715±328</td>
</tr>
</tbody>
</table>
The attenuation of x-rays through matter depends on both, the composition of matter and the energy of the incident x-rays. Therefore, DECT has the potential to provide additional information for characterization of plaque. Plaque components could be discriminated if the difference in attenuation between the two energies is significant.

5.3 MDCT in coronary calcium measurements

The quantification of coronary artery calcium with CT is well established. Calcium scores are typically measured from non-contrast images, acquired sequentially. Reconstructed CT images are first segmented using a predetermined threshold to discard non-calcium pixels. Calcium is then quantified from the segmented images. The most commonly used calcium scoring methods are Agatston scoring, volume scoring and mass scoring (60, 61). Calibration phantoms may also be used along with the scans to determine scan-specific calibration factors for mass measurements (62).

In some cases it would be advantageous to quantify calcium from a contrast-enhanced CT scan of the coronaries. In a study to evaluate the validity of calcium scores determined from contrast-enhanced scans, Muhlenbruch et al (63) found that the Agatston scores were higher than that of non-contrast scans. This effect is likely due to iodinated contrast in the lumen, which cannot be adequately separated from calcium, and therefore, falsely increases the calcium score.

The potential use of DECT has been demonstrated for several non-cardiac applications (64): renal stones (24), bone removal (65), aneurysm (66, 67). The application of DECT in separating calcium from iodine has been demonstrated in phantoms (68, 69) and ex-vivo (70). Therefore, DECT has the potential to improve
calcium quantification from contrast-enhanced images. Attenuation information from both the x-ray energies can be used to separate calcium from iodine in the vessel lumen. Also, an advantage of DECT is that high image contrast can be maintained due to the lower x-ray energy while minimizing partial volume averaging (blooming) artifacts at the higher x-ray energy. The rationale being blooming artifact is observed in highly attenuating components and lower tube voltages. Hence, calcifications will appear to have larger sizes at 80 kVp as compared to 140 kVp while the lumen and stenosis area measurements will not change significantly.

DECT can be used to create virtual non-contrast images (VNC). Calcium can then be quantified from such images using traditional scoring methods: Agatston, volume and mass scoring.

### 5.3.1 Calcium scoring methods

Calcium scoring methods first separate or segment the calcified regions from the surrounding tissue. The method of segmentation used is called thresholding and is based on either the attenuation (HU-based) or density of the tissue. The attenuation-based threshold is a simple CT number value above which pixels are identified as calcium. Typically this value is 130 HU at 120 kVp derived as the mean attenuation of blood in the lumen plus twice the standard deviation (mean+2*SD) (60). The fixed density threshold is a measure of the concentration of calcium and, therefore, is invariant across tube voltages scanners, patient sizes and calibration factors. A density of 100 mg/mm³ calcium HA is recommended (71).
**Agatston scores**

Agatston scoring method was developed specifically for EBCT (60). It is a non-linear weighting method developed for scoring coronary calcium from 3 mm thick slices acquired at 130 kVp in sequential scans. The Agatston score ($S_{ij}$) is calculated from the area of each segmented calcified lesion ($A_{ij}$) multiplied with a weighting factor ($w_{ij}$) that is dependent on the attenuation of the lesion:

$$S_{ij} = w_{ij} \times A_{ij} \ldots \text{Equation 11}$$

$$W_{ij} = 1 \text{ for } 130 – 200 \text{ HU}$$
$$= 2 \text{ for } 200 – 300 \text{ HU}$$
$$= 3 \text{ for } 300 – 400 \text{ HU}$$
$$= 4 > 400 \text{ HU}$$

To obtain equivalent Agatston values with MDCT scanners, the slice thickness and attenuation at the tube voltage must be adjusted (72). The image noise depends on the slice thickness. Further, the weighting factor will change for different tube voltages non-linearly. Therefore, this method of scoring is highly dependent on the scanner type and scan-protocols used, and hence, needs significant adjustment for different scanners and scan-protocols. However, Agatston scoring is widely accepted clinically since it has been used for a long time and a significant amount of literature is available on the interpretation of the scores.
Volume scores

The total volume number of high intensity voxels \( N_{\text{voxel}} \) above a set threshold multiplied by the size of each voxel is the calcium volume score.

\[
V = V_{\text{voxel}} * N_{\text{voxel}} \quad \text{Equation 12}
\]

The volume score is dependent on the threshold selected and is particularly sensitive to the slice thickness and partial volume artifacts. Hence, the volume score is an overestimation of the true calcium volume (71, 72).

Mass scores

Mass scores (measured in mg) are computed from the volume \( \text{cm}^3 \) and density \( \text{mg/cm}^3 \) of the segmented calcium.

\[
\text{Mass} = \text{Density} * \text{Volume} \quad \text{Equation 13}
\]

Calcium attenuation is proportional to the density of calcium. The density of calcium is measured in reference to the attenuation of 200 mg of CaHA/cc scanned at the same tube voltage. Using a phantom (200 mg of CaHA/cc and water), a calibration factor \( c \) (measured in mg/cm\(^3\)*HU) is computed for the attenuation of calcium of density \( \rho_{\text{CaHA}} \) at a particular x-ray energy with respect to water.

\[
c = \frac{\rho_{\text{CaHA}}}{(\text{CT\#}_{\text{CaHA}} - \text{CT\#}_{\text{Water}})} \quad \text{Equation 14}
\]

\[
\text{Mass} = c * \text{CT\#} * \text{Volume} \quad \text{Equation 15}
\]
Mass scores are, therefore, independent of x-ray energy. These scores like volume scores are dependent on the segmentation threshold and this threshold has to be adjusted across tube voltages to result in equivalent scores. The use of a density threshold as opposed to an attenuation based threshold has been recommended (71). Partial volume averaging artifact, which significantly affects calcium volume scores, does not affect the mass score. When an object partially covers a voxel, its attenuation is averaged over the entire voxel. Therefore, the voxel has lower attenuation than the attenuation of the object in its path. But the mass remains constant. Hence, the mass scores are considered to be most robust calcium quantification method (72).

5.4 Micro Computed Tomography

A microCT system consists of a polychromatic x-ray source and a detector system mounted on a gantry. The system used for the work described in this dissertation, has a tube voltage range of 35 to 80 kV and x-ray current 100 – 400 µA. The gantry rotates through 360° stopping in small increments to acquire a single projection. The angle of increment can be adjusted in increments of 0.1 to 5.0°. The detector system consists of a scintillator and a CCD (charge coupled device) camera. The x-rays through the specimen create a radiographic projection on the scintillator that is recorded by the camera. The analog signal from the camera is then digitized for image reconstruction. The system also allows averaging of frames per projection to improve SNR.

The maximum spatial resolution available is 27 x 27 µm with minimum slice thickness of 27 µm. After reconstruction the image data is represented in intensity values. These values have to be converted to meaningful CT numbers. This is done using a
calibration phantom that consists of air, a water bubble and bone (CaHA). Values from the calibration are used in an equation similar to that used with clinical CT for the calculation of CT numbers:

\[
CT\# = \frac{\mu - \mu_{\text{water}}}{\mu_{\text{water}} - \mu_{\text{air}}} \quad \text{…Equation 16}
\]

MicroCT offers the highest spatial resolution among x-ray based imaging systems. Hence, it is possibly the best x-ray based modality for ex-vivo coronary plaque imaging. Langheinrich et al (73) studied imaging of the arterial wall using microCT in comparison to histology. A total of 65 microCT images were matched to histology sections, from 10 human coronary arteries. MicroCT was performed at x-ray tube energy of 40 kVp and reconstructed to give a maximum spatial resolution of 8 μm and slice thickness of 6 μm. Histology sections were 5 μm thick at every 5 mm of the embedded tissue. In their findings, microCT was able to depict all the plaques identified in histology along with early fatty lesions. However, classic Hounsfield units were not reported in the above study due to the absence of a calibration block.

When compared to histology, microCT offers rapid, whole vessel analysis of unprocessed coronary arteries. Subsequently reducing errors in lesion matching and avoiding loss of information due to decalcification and sectioning. Moreover, with necessary calibration to classic HU values, plaque measurements at tube voltages as low as 40 kVp can be made. Hence, microCT imaging can be used to evaluate the potential application of dual energy x-rays for identification of plaque components.
6.1 Development of Dual Energy CT protocol for plaque characterization

A dual-energy scan protocol for imaging coronary arteries ex-vivo on a dual source CT scanner was developed using a water phantom. Details of the protocol used for plaque characterization is included in chapter VI. This section describes the method to developing the protocol. The manufacturer default protocol was modified so that noise was minimized in the reconstructed images. A water phantom of 20 cm diameter was used for noise measurements. Noise was estimated as the standard deviation (SD) of the mean attenuation in a region-of-interest (ROI). The following were evaluated:

- Effect of field-of-view (FOV) and ROI sizes on noise
- Effect of tube current on noise at each tube voltage
6.1.1 Effect of field-of-view size and region-of-interest size on noise

To study the effect of FOV size on noise in the reconstructed image, single energy scans of a water phantom were acquired with tube voltage 120 kVp and tube current varying from 30 – 290 mAs/rot. Images were reconstructed using two FOVs: small (50 mm) and large (200 mm). Other reconstruction parameters were kept constant and included a reconstruction kernel (B35f) with cutoff of 9.3 lp/cm and reconstructed slice thickness of 0.6 mm with an image increment of 0.3 mm.

Four ROIs of varying sizes were used to measure noise. The ROIs were defined by the number of pixels in each; very small (20 pixels), small (100 pixels), medium (506 pixels) and large (4000 pixels). The pixel size can be calculated from the FOV and image matrix size:

\[ \text{Pixel} = \frac{\text{FOV}}{\text{MatrixSize}} \quad \ldots \text{Equation 17} \]

Hence, for a 50 x 50 mm\(^2\) FOV each pixel measures 0.097 mm on a side and for a 200 x 200 mm\(^2\) FOV each pixel measures 0.39 mm on a side with a standard 512 x 512 image matrix.

The x-y resolution of a CT image depends on the scanner hardware (e.g. detector element spacing, detector width) and the reconstruction kernel. The highest in-plane resolution that can be achieved with the dual source scanner is 0.4 mm x 0.4 mm. Therefore, the pixel size for a FOV of 200 x 200 mm\(^2\) approximately matches the maximum x-y resolution of the scanner.

Noise in the small FOV, then, is lower than noise in the large FOV for the same number of pixels (Figure 6-1) because each pixel in the small FOV has a resolution less
than the minimum in-plane resolution of the scanner. The reconstruction algorithm interpolates x-ray quanta registered by the detectors and approximates values for pixels in the image. As the x-y resolution of the image falls below the minimum in-plane resolution of the scanner, the pixel values become more dependent on the approximations made by the reconstruction algorithm, than the “true” quanta measured by the detectors.

As seen in Figure 6-1, the noise measured from large FOV images remains relatively constant except for the very small ROI. Also, mean attenuation measured in these images was near 0 HU for all ROIs as expected for water. For the very small ROI, the pixels are too few to represent the true quantum measured by the detectors and the reconstruction algorithm dominates. As a result, the image appears smoother than it actually is. Also, the mean attenuation values are not nearly 0 HU. Hence, we can conclude that the noise measured in large FOV is more accurate provided the ROIs used are large enough. Thus, it was decided that a FOV of 200 x 200 mm would give most accurate measurements of plaque attenuation in the coronaries.
Figure 6-1. Comparison between large FOV (200 mm) and small FOV (50 mm) with ROIs of 20, 100, 506 and 4000 pixels. DS scans at a single energy (120 kVp, 90 mAs/rot), temporal resolution of 83 ms, collimation of 32 x 0.6 mm and pitch of 0.28.

6.1.2 Effect of tube current on noise at varying tube voltages

To study the effect of tube current on noise, three different protocols were used: a cardiac dual source with single energy (DS) and a non-cardiac dual-energy (DE). DS scans were performed at all available tube voltages (80, 100, 120, and 140 kVp). Tube currents were increased in fixed steps from the lowest to the highest allowable at a given tube energy. For DE protocol, tube energies were selectable was in pairs (140/80 kVp and 140/100 kVp). For this experiment, the current across one tube was kept constant.
while the other was varied. Measurements were made from the images with varying tube current only. DS protocol splits the required tube current between the two tubes while the tube current across each tube can be individually controlled in the DE protocol (16).

All images were reconstructed at a FOV of 200 x 200 mm$^2$ with a reconstructed image thickness of 0.6 mm and a reconstructed image increment of 0.3 mm. A manufacturer specific medium smooth reconstruction kernel (B25f) was used.

When the tube current is increased the number of x-rays produced is increased allowing more x-ray quanta to reach the detectors. Also, increasing the tube voltage increases the energy of x-rays, resulting in better penetration and less scatter. As a result, noise in the image is decreased. This is confirmed in Figure 6-2 and Figure 6-3. However, the noise in DS scans is higher than the noise in DE (Figure 6-4). This is due to differences in the number of projections used for image reconstruction: DS uses 180° of parallel projections and DE scans use 360° of parallel projections. Further, as the tube current in a DS protocol is divided equally over two tubes, each set of detectors receive nearly half of the total emitted x-rays. This decreases the SNR, potentially resulting in the increased noise observed.

For the purpose of imaging coronary arteries ex-vivo, the tube current-time product value at each tube voltage was selected such that the resultant noise in water was the same across all tube voltages. The DS scans were optimized to produce image noise corresponding to the least noise in the 80 kVp image. The lowest possible noise level was 50 HU. Tube current-time products at respective tube voltages corresponding to this noise level were selected from Figure 6-2 (140/90, 120/90, 100/170, and 80/330 kVp/
mAs/rotation). Similarly, values for DE scans for minimum SD of ~30 were 140/30, 100/70, 80/165 kVp/MA/rotation (140/75, 100/175, 80/412 kVp/eff. mAs; Figure 6-3).

Figure 6-2. Measurements of noise (standard deviation, SD) in a water phantom for all available tube voltages; 80, 100, 120 and 140 kVp. Dual source single energy cardiac protocol (ECG-gated) with parameters of tube currents 30 – 330 mAs/rotation, beam collimation 32 x 0.6 mm, temporal resolution 83 ms and pitch 0.28. Dashed line indicates the least noise level, matched across all tube voltages.

As the tube current is increased the number of x-rays produced is increased hence the noise is decreased. Also, increasing the tube voltage increases the energy of x-rays,
resulting in better penetration and less scatter decreasing the noise in the image. This is confirmed in Figure 6-2.

Figure 6-3. Measurements of noise (standard deviation, SD) in a water phantom for all available tube voltages; 80, 100 and 140 kVp. Dual-energy scan protocol (non-cardiac) with parameters of tube currents 20 – 165 mAs/rot (50 – 412 effective mAs), collimation 32 x 0.6 mm, temporal resolution 330 ms and pitch 0.4. Dashed line indicates the least noise level, matched across all tube voltages.

### 6.1.3 Comparison of noise in a dual source scanner

The noise characteristics of the dual source CT scanner were compared to a single source CT scanner using the same scan protocol described above. As seen in Figure 6-4,
the noise resulting from a dual source single energy (DSSE) scan is higher than the noise in both a dual source dual energy (DSDE) and a single source (SS) of the two available sources. This is because of the number of projections used for reconstructing the images. The cardiac protocol (DSSE and SSSE) use 180° (half-scan reconstruction) whereas the non-cardiac protocols (DSDE and SS) use 360° (full-scan reconstruction).

Figure 6-4. Comparison of noise at 140 kV across the whole range of effective mAs using a single tube of a dual tube scanner (SS), dual tube with single energy (DSSE), dual tube dual energy protocol (DSDE) and single tube (SSSE) on a conventional scanner.
6.2 Development of dual-energy CT protocol for calcium scoring

In contrast to most clinical calcium scoring protocol that uses sequential scanning, we used spiral mode of acquisition. All scans were synchronized to a simulated ECG signal. Water phantom scans were again used to optimize noise in reconstructed images. Specifically, the goal was to achieve least possible noise in the images and, also, to match the noise in images across all tube voltages. Hence, no dose saving protocols, including ECG-based tube current modulation, were used. Our reference standard was a single energy scan at 120 kVp, the tube voltage clinically. For dual-energy scanning the widest range of tube voltages available on the scanner was selected (80 and 140 kVp) to maintain the differences in attenuation values and therefore, improve calcium-iodine identification. Because the lowest x-ray energy determines the minimum achievable image noise, the tube-current for the lowest tube voltage, i.e. 80 kVp (tube B), was selected to be the maximum allowable (181 mAs/rotation). The tube current for the high tube voltage i.e. 140 kVp (tube A) was increased in fixed increments to achieve the same noise (~ 45 HU) in the reconstructed 80 and 140 kVp images (Figure 6-5). Tube current in the single energy (120 kVp) scans was also selected to match this noise level. So that noise in all images was equivalent. To reduce partial volume averaging artifact, thin slices (0.6 mm) were reconstructed with a 0.3 mm slice increment. All scans were reconstructed with a kernel dedicated for calcium quantification (B35f).
Figure 6-5. Measurements of noise (standard deviation, SD) in a water phantom for tube voltages; 80 and 140 kVp. Dual-energy scan protocol (cardiac) with parameters of tube currents 20 – 165 mAs/rot (50 – 412 effective mAs), collimation 32 x 0.6 mm and temporal resolution 165 ms. Dashed line indicates the least noise level, matched across all x-ray tube voltages.

6.3 Experimental Setup

A perfusion system for imaging coronary arteries ex-vivo with CT was developed (Figure 6-6). The coronary vessel is placed in a plastic container that has two holes on opposite walls (Figure 6-7). The smaller hole is fixed with an introducer that is inserted into the coronary ostium for the administration of saline and contrast agent during scanning. The large hole is fitted with a tube to drain out all the fluids that accumulate in the container. The vessel is pinned and secured on wax before imaging. It is then
continuously perfused with saline (PBS); pressure of flow is maintained using a nitrogen tank and a pressure gauge mounted on the saline tank. Contrast is introduced into the vessel whenever needed through a Y-connector, using a power injector (Medrad Inc, PA, USA).

![Diagram of experimental setup](image)

Figure 6-6. Schematic of experimental setup for CT imaging of coronary arteries ex-vivo.

![Container showing placement of coronary vessel](image)

Figure 6-7. Container showing placement of coronary vessel.

### 6.4 Development of contrast injection protocol

To standardize the contrast enhancement across tube voltages, preliminary scans were performed. The objective was to maintain lumenal enhancement within a clinically desirable range (250 - 350 HU). The injection protocol had to be adjusted to
accommodate several issues not normally encountered in clinical scans. First, as the there is no tissue or a phantom simulating the human thorax around the vessel, there are more photons penetrating the coronary artery. There is also less influence of scatter on the images. Hence, slight changes in the concentration of contrast material result in large differences in attenuation. Second, contrary to in-vivo blood flow, the flow rates and volumes of saline in the ex-vivo system are much smaller and therefore, more sensitive to the rate of contrast injection. Through multiple trials using a coronary artery the optimal rate of contrast injection was found to be 0.1 ml/sec using 270 mg of I/l contrast agent (Ultravist 270, Berlex, USA). This flow rate was the minimum available on the automated contrast injection system. Hence, if further reduction in lumenal enhancement was needed for a given coronary artery, contrast was diluted with saline prior to contrast injection. The percentage of dilution varied from individual vessels as the morphology of each vessel was unique.

6.5 Development of MicroCT imaging protocol

A phantom representing different tissue densities was scanned using a microCT scanner (Explore Locus, GE, Milwaukee, WI). The phantom was made of individual cylindrical inserts of 1 cm diameter and 0.5 cm length with densities representing adipose tissue (0.94 mg/cc), low-density soft tissue (0.65 mg/cc), muscle (1.08 mg/cc) and spongy bone (1.2 mg/cc HA). The inserts were enclosed in a cylinder representing tissue. A calibration phantom with a water equivalent material, air bubble and calcium (hydroxyapatite, HA) were also scanned with the phantom.
Figure 6-8. Image of the tissue phantom acquired using clinical CT. Circular inserts represent “tissue” of different densities: Low density soft tissue (red arrow), adipose (blue arrow), muscle (yellow arrow) and spongy bone (white arrow).

Three scans were performed using tube voltages of 40, 60 and 80 kVp. At a tube voltage of 40 kVp, the maximum available tube current of 500 uA was used to compensate for low penetration at this x-ray energy. At tube voltages of 60 and 80 kVp, tube currents were 400 uA and 150 uA, respectively. For each image, 360 views were acquired at every 1° increment averaged over 2 frames (data acquisitions). Acquisition time for each view was 4 s. All data was acquired at an isotropic resolution of 27 um. Data were reconstructed using a Feldkamp cone beam kernel to generate a single volume. Data from each scan were calibrated to classical CT attenuation values (Hounsfield units, HU) using water and air values from the calibration phantom. Therefore, the CT number of water at each tube voltage was expected to be 0 HU.

The phantom was also scanned on a clinical CT scanner (SOMATOM Definition, Seimens, Erlangen) using a dual-energy protocol (80/140 kVp). Details of this protocol are in section 5.2. Measurements of attenuation in HU were made in each phantom insert.
from microCT images acquired at 40, 60 and 80 kVp and clinical CT images acquired at 80 kVp.

Similarity in x-ray attenuation from the two modalities was estimated by comparing attenuation values from 80 kVp images from both systems with one-way ANOVA and Tukey’s HSD test for multiple pairwise comparisons. To evaluate if any one tube voltage could sufficiently discriminate between the inserts, mean attenuation between inserts were compared using one-way ANOVA and Tukey’s HSD test for multiple pairwise comparisons for given tube voltage and scanner.
Table 6-i. Attenuation values measured from the tissue phantom.

<table>
<thead>
<tr>
<th>Tube Voltage (kVp)</th>
<th>Attenuation values (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low density soft tissue</td>
</tr>
<tr>
<td>80 (clinical CT)</td>
<td>-410 ± 5.8</td>
</tr>
<tr>
<td>80 (microCT)</td>
<td>-476 ± 3.3</td>
</tr>
<tr>
<td>60 (microCT)</td>
<td>-502 ± 2.3</td>
</tr>
<tr>
<td>40 (microCT)</td>
<td>-567 ± 1.4</td>
</tr>
</tbody>
</table>

Using any single x-ray energy with microCT, significant differences in attenuation were observed between all tissue types. Data at 80 kVp tended to show lower contrast (measured as difference from water at 0 HU) in the tissue phantoms compared to data at 40 kVp (Figure 6-9). Further, differences in attenuation between 80 and 40 kVp were statistically significant for all tissue phantoms.

Using the clinical CT system, attenuation values measured from 80 kVp images were significantly different across all tissue phantoms. However, HU values did not match those obtained with microCT at 80 kVp (Table 6-i).
Figure 6-9. Attenuation values of low density soft tissue, adipose, muscle and bone measured from microCT and clinical CT images.

Attenuation values measured from clinical CT images at 80 kVp were significantly different from values measured from microCT images at 80 kVp for all tissues. These differences could be due to a number of factors including differing x-ray spectra, reconstruction kernels, detector technology between clinical and microCT. Although the peak voltages produced by both the modalities at 80 kVp is the same, the mean energies of the x-ray spectra could differ and, thus produce differing patterns of x-ray interactions with tissue and differing x-ray attenuations. Noise in the microCT images is further influenced by microCT detector technology, which is more sensitive to noise than the detectors used for clinical CT. To reduce the influence of noise, each projection was averaged with two frames. Noise measured from the microCT images was 421, 231
and 320 HU at 40, 60 and 80 kVp. Finally, the calibration phantom provided by the manufacturer for calibrating microCT images used a water equivalent material. Using liquid water may change the HU values measured from microCT images.

Due to the differences in attenuation values from the two modalities, attenuation values from microCT were not compared to CT for tissue imaging. Also, 2 frames provided best compromise between image acquisition time and noise. Calcium phantoms with density higher than spongy bone caused severe artifact in the surrounding especially with decrease in tube voltage. Therefore, calcified and stented vessels were avoided for microCT scanning. Further, because of the rather extending time required for scanning, tissue was fixed before scanning to avoid degradation.
CHAPTER VII

POTENTIAL OF DUAL-ENERGY COMPUTED TOMOGRAPHY TO CHARACTERIZE ATHEROSCLEROTIC PLAQUE: EX VIVO ASSESSMENT OF HUMAN CORONARY ARTERIES IN COMPARISON TO HISTOLOGY.

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Specific aim 1: To characterize coronary atherosclerotic plaque using dual-energy computed tomography.

In this chapter, the potential application of dual-energy computed tomography (DECT) for identification and classification of coronary atherosclerotic plaque is evaluated using excised human coronary arteries. The experimental methods, results and a discussion based on these findings are included.

7.1 Abstract

Background: Non-invasive characterization of coronary atherosclerotic plaque is limited with current CT techniques. DECT has the potential to provide additional attenuation data for better differentiation of plaque components.

Objective: To characterize coronary atherosclerotic plaque using dual-energy computed topography (DECT).

Methods: Seven human coronary arteries acquired at autopsy were scanned consecutively at 80 and 140 kVp with CT. Vessels were perfused with saline and data were acquired before and after contrast agent injection. Lesions were identified and attenuation measurements were made from CT image quadrants. CT quadrants were classified as densely-calcified, fibro-calcific, fibrous, lipid-rich or normal vessel wall corresponding to matched histology images. Attenuation values at each kVp were compared within plaque types for both non-contrast and contrast scans. Further, Dual Energy Index (DEI) values computed from attenuation were analyzed for classification of plaque.

Results: In 14 lesions, a total of 56 quadrants were identified. Histology results classified 8 (14%) as densely-calcified, 8 (14%) as fibro-calcific, 9 (16%) as fibrous, 5 (9%) as
lipid-rich, and 25 (45%) as normal vessel wall from non-contrast images. Calcified lesions attenuated significantly more at 80 kVp in both contrast and non-contrast scans whereas fibrous plaque attenuated more at 80 kVp only for contrast-enhanced scans. No differences were found for lipid-rich plaques. Using DEI values only densely-calcified plaques could be distinguished from other plaque types except fibro-calcific plaques in contrast images.

Conclusions: Only densely-calcified and fibro-calcific plaques demonstrated a true change in attenuation at 80 versus 140 kVp. Therefore, calcified plaques could be distinguished from non-calcified plaques with DECT but further classification of plaque types was not possible.

7.2 Introduction

Most acute coronary syndromes are initiated by the rupture of “vulnerable” lesions. Histologic characteristics of these lesions have been described in previous post-mortem studies (1). The in-vivo characterization of different atherosclerotic plaque components might allow the identification of high-risk lesions before events occur.

CT using a single x-ray energy has been evaluated in phantoms (2), ex-vivo in excised human hearts (3-7) and in-vivo in humans (8-19) and animals (20) for the identification and classification of coronary artery plaque. Some studies have demonstrated the possibility of plaque classification based on attenuation values measured in Hounsfield Units (HU) (3-5, 18). However, clinical application is limited by considerable overlap in HU values among different plaque components (19). These
results likely reflect variations in the composition of specific plaque components, particularly non-calcified lesions that yield x-ray attenuation values spanning a wide range.

The application of dual energy CT (DECT) where attenuation data are acquired at two peak x-ray tube voltages (rather than a single peak x-ray tube voltage as with traditional CT imaging), to coronary artery imaging has the potential to better characterize atherosclerotic plaque (21). The combined attenuation data may prove more accurate for discriminating plaque components. DECT techniques have been studied since the late 1970s (22, 23) but have only recently become available on clinical CT systems for cardiac imaging. DECT has been applied to imaging of the liver for detection of fat (24), lumbar spine for bone mineral density measurements (25), and the brain for detection of tumors (26) but the utility of DECT for coronary plaque characterization is unknown.

The purpose of this work was to determine if DECT can differentiate and, therefore, classify coronary atherosclerotic plaque components based on imaging human coronary arteries ex-vivo with direct comparison to histology.

7.3 Methods

7.3.1 Vessel Preparation

The entire human left anterior descending (LAD) coronary artery including the coronary ostium and 40 mm surrounding tissue was excised from seven hearts acquired at autopsy (7). Vessels were refrigerated at all times before fixation (vessels were fixed
within 72 hours of autopsy) except while imaging. The study was approved by the local Institutional Review Board.

The proximal end of the LAD was cannulated, the distal end was left open, and side-branches were ligated. The vessel was fixed to a wax base to restrict movement during scanning. In an initial step, intravascular ultrasound (IVUS) was used to identify lesion sites with focal atherosclerotic plaque. Radio-opaque markers were placed externally on the heart tissue surrounding the LAD at each lesion site to allow matching to CT images and histology.

7.3.2 Experimental CT Imaging Setup

The prepared vessel was imaged with CT within 48 hours after autopsy and prior to fixation. A previously validated and described pressure perfusion model was used for ex-vivo CT imaging of the coronary arteries (Figure 7-1) (7). This model allows continuous perfusion of saline through the vessel lumen under controlled pressure, maintained within physiological limits. The vessel holder was designed to allow injection of saline into the cannulated ostium and draining of saline from the distal LAD into a waste container. The model also allowed injection of contrast into the saline stream via an automated contrast injector.
7.3.3 Dual Energy CT

The entire LAD was scanned using a clinical dual source CT scanner (Definition, Siemens Medical Solutions, Erlangen, Germany). The CT system allowed a minimum peak tube voltage of 80 kVp and a maximum of 140 kVp. The acquisition of data during simultaneous application of two different x-ray energies was not available for cardiac imaging at the onset of this study. Therefore, data were acquired consecutively first at 80 kVp and then at 140 kVp. The tube current was adjusted to maintain a similar noise level (measured as the standard deviation of signal from a water phantom) at the minimum and maximum voltages. The tube current required at 80 and 140 kVp to achieve a standard deviation of 50 HU in water was 330 and 90 mAs/rot, respectively (Figure 7-2). Other scan parameters were kept constant: gantry rotation time = 330 ms, beam collimation = 32 x 0.6 mm, reconstruction slice thickness = 0.6 mm with 0.3 mm overlap and reconstruction kernel = medium smooth (B35f with a cutoff of 9.3 lp/cm).
Figure 7-2. Measurements of noise (standard deviation, SD) in a water phantom for all available tube currents at peak tube voltages of 80 kVp (●) and 140 kVp (▲) from dual source CT images acquired consecutively using ECG-gated spiral techniques. Other scan parameters included 32 x 0.6 mm beam collimation, 330 ms gantry rotation time, 0.28 pitch. Horizontal line indicates the lowest noise level achievable at both tube voltages.

The vessel was continuously perfused with saline at constant pressures that ranged from 100 mmHg to 140 mmHg. As previous studies have reported an increase in the attenuation of the vessel wall due to the presence of contrast (2,6,7,27), scans were first performed without contrast and then repeated during contrast injection to evaluate the effects of contrast on attenuation measurements. Contrast agent with an iodine concentration of 270 mg I/ml (Ultravist 270, Berlex Inc., New Jersey, USA) was injected into the saline stream at a flow rate of 0.1 ml/s during the entire scan. The resulting lumenal enhancement ranged from 250 - 400 HU at 80 kVp and from 150 – 250 HU at 140 kVp in an attempt to achieve attenuation values corresponding to a 250 – 350 HU range at 120 kVp (the preferred attenuation range for clinical coronary CT images).
7.3.4 Histology

After completion of all imaging procedures, the vessels were fixed in 10% buffered formalin solution using a perfusion system with fixed pressure and flow of formalin through the vessel. After decalcification, if needed, the vessel was embedded in paraffin such that cross sections through the vessel were orthogonal to the vessel axis. Using a microtome, 5 µm thick sections were taken every 20 µm at each lesion site identified and marked before fixation based on IVUS imaging. Typically, 5 – 7 pairs of slides were prepared from each lesion. Histology sections were stained with hematoxylin and eosin (H&E) and with Movat pentachrome stains.

Plaque components were identified by an experienced scientist (A.N.) blinded to the CT results using the Movat stains as the gold standard for tissue characterization. For the purpose of plaque characterization, lesions were identified by their most clinically significant regions using a modified Stary classification (28, 29). Lesions were divided into quadrants for more precise identification of plaque components. Plaques were identified as densely-calcified, fibro-calcific, fibrous, fibro-fatty and necrotic core. For the purpose of CT matching, fibro-fatty and necrotic core were combined as lipid-rich plaques. Histology scans were oriented to match CT images.

7.3.5 Data Measurement and Analysis

CT images were reformatted orthogonal to the vessel axis. Lesion sites were identified using the radio-opaque markers and anatomical landmarks in comparison to saved IVUS images (P.S.). The CT image at each lesion site was divided into quadrants.
for more accurate identification of plaque components (Figure 7-3). Side-by-side review of the non-contrast and contrast-enhanced images at the same window/level allowed delineation of the lumen and outer vessel border in the non-contrast enhanced images. Circular ROIs (ranging in size from 10 – 24 pixels) were placed in the vessel wall in each quadrant on non-contrast and contrast-enhanced CT images obtained at 80 and 140 kVp and the mean and standard deviation of the attenuation recorded. Corresponding attenuation values measured at 80 and 140 kVp were combined to create a dual energy index (DEI) in an attempt to increase the sensitivity of dual energy data for detecting differences in plaque components. The DEI is a ratio of the difference in HU values at the two peak voltages to their sum; individual attenuations are shifted by 1000 HU to avoid negative values:

\[
DEI = \frac{(x_{80} + 1000 \text{ HU}) - (x_{140} + 1000 \text{ HU})}{(x_{80} + 1000 \text{ HU}) + (x_{140} + 1000 \text{ HU})}
\]

\[
DEI = \frac{x_{80} - x_{140}}{x_{80} + x_{140} + 2000 \text{ HU}}
\]  

… Equation 18

where \( x_{80} \) and \( x_{140} \) are the measured attenuation at 80 kVp and 140 kVp, respectively.

### 7.3.6 Statistical Analysis

The number of samples for this pilot trial was simply based on the number of available vessels within a six-month period. Attenuation values at 80 and 140 kVp were compared separately for non-contrast and contrast images to determine if changes in peak tube voltage caused detectable changes in plaque attenuation. A nonparametric sign test,
modified for correlated data (i.e. multiple lesion sites per artery), was performed for each plaque type to test whether one peak voltage tended to produce higher attenuation than the other. A p-value < 0.05 indicated statistical evidence of a bias. Both non-contrast and contrast derived DEI values were then compared separately among plaque components using a one-way ANOVA and Tukey's HSD test for multiple pairwise comparisons to determine if dual energy data could be used to discriminate plaque types.

Figure 7-3. Non-contrast enhanced CT images acquired consecutively at peak tube voltages of 80 kVp (left) and 140 kVp (center). Coronary arterial cross-sections (within dashed lines) were divided into quadrants with upper and lower right quadrants classified as densely-calcified and upper and lower left quadrants classified as normal vessel wall from histology (right). CT images were acquired as consecutive scans.

Attenuation values were also compared before and after contrast administration for each plaque type to determine if plaque and vessel wall enhancement, in addition to lumenal enhancement, could be observed in the presence of contrast. A sign test, modified for correlated data, was again used with a p-value < 0.05 indicating introduction of bias in plaque measurements as a result of contrast administration.
7.4 Results

Seven vessels with a total of 14 lesions (56 quadrants) were scanned. Histologic results classified 8 quadrants (14%) as densely-calcified, 8 (14%) as fibro-calcific, 9 (16%) as fibrous, 5 (9%) as lipid-rich and 26 (46%) as normal vessel wall. All lesions were visible on non-contrast enhanced images but one lesion could not be identified from contrast-enhanced data due to improper selection of scan range. Therefore, four of the 56 quadrants (two lipid rich, two normal vessel wall) were evaluable only on non-contrast enhanced images reducing the number of lipid-rich plaques evaluated from these images to three.

Table 7-i. Comparison of the attenuation of plaque types measured from non-contrast images at peak tube voltages of 80 kVp and 140 kVp.

<table>
<thead>
<tr>
<th>Pathology Type</th>
<th>Attenuation at 80 kVp (HU)</th>
<th>Attenuation at 140 kVp (HU)</th>
<th>Difference (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Densely-calcified</td>
<td>599.2 (420.3)</td>
<td>455.6 (332.4)</td>
<td>143.7 (101.1)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fibro-calcific</td>
<td>156.1 (177.7)</td>
<td>127.4 (127.3)</td>
<td>28.7 (54.7)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fibrous</td>
<td>19.6 (21.4)</td>
<td>11.9 (25.7)</td>
<td>7.7 (13.1)</td>
</tr>
<tr>
<td>Lipid-rich</td>
<td>9.11 (37.2)</td>
<td>8.7 (40.4)</td>
<td>0.4 (5.2)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation). Difference is the mean of pairwise differences.

* Statistically different from 0 at p = 0.005 according to sign test.
† Statistically different from 0 at p = 0.008 according to sign test.
7.4.1 Comparison of Attenuation at 80 and 140 kVp from Non-contrast Enhanced Images

Comparison of HU values measured from non-contrast 80 and 140 kVp images demonstrated a significantly higher attenuation for densely-calcified (p = 0.008) and fibro-calcific (p = 0.005) plaques at 80 kVp but no change in the attenuation of fibrous and lipid-rich plaques (n = 5) (Table 7-i). DEI values computed using non-contrast attenuation measurements (densely-calcified: 0.043 ± 0.026; fibro-calcific: 0.010 ± 0.020; fibrous: 0.004 ± 0.007; and lipid-rich (n =5): 0.003 ± 0.003) could be used to discriminate densely-calcified plaques from all other plaque types (overall type I error < 0.05, Tukey’s HSD test). However, fibro-calcific and non-calcified plaques could not be distinguished nor could subgroups of non-calcified plaques (fibrous, lipid-rich) be distinguished on the basis of non-contrast DEI values (Figure 7-4a).
Figure 7-4. a) Dual Energy Index (DEI) values calculated using attenuation values measured from non-contrast scans. Values display considerable overlap in all except densely calcified plaques. b) DEI Dual Energy Index (DEI) values calculated using attenuation values measured from contrast scans. Values display considerable overlap in all plaques.
7.4.2 Comparison of Attenuation Values Before and After Contrast Administration

For most plaque types, attenuation measurements from contrast-enhanced images demonstrated an increase both at 80 and 140 kVp compared to measurements from non-contrast images ($p \leq 0.016$). However, lipid-rich plaques ($n=3$) at both 80 and 140 kVp and densely-calcified plaque at 140 kVp (Table 7-ii) did not enhance after contrast administration.

Table 7-ii. Attenuation values of plaque without introduction of contrast and in the presence of contrast agent at peak tube voltages of 80 kVp and 140 kVp.

<table>
<thead>
<tr>
<th>Pathology Type</th>
<th>Attenuation at 80 kVp (HU)</th>
<th>Attenuation at 140 kVp (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>w/o contrast</td>
<td>w/ contrast</td>
</tr>
<tr>
<td>Densely-calcified</td>
<td>599.2 (420.3)</td>
<td>738.8 (419.6)</td>
</tr>
<tr>
<td>Fibro-calcific</td>
<td>156.0 (177.7)</td>
<td>267.1 (182.8)</td>
</tr>
<tr>
<td>Fibrous</td>
<td>19.6 (21.4)</td>
<td>79.6 (53.0)</td>
</tr>
<tr>
<td>Lipid-rich</td>
<td>9.11 (37.2)</td>
<td>74.3 (68.8)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation). Values were compared using a sign test modified for correlated data where $p < 0.05$ indicates significance.

7.4.3 Comparison of Attenuation Values at 80 and 140 kVp for Contrast-Enhanced Images

Comparison of HU values measured from contrast-enhanced 80 and 140 kVp images demonstrated a significantly higher attenuation for the lumen and all plaque types.
at 80 kVp, except for lipid-rich plaque (n = 3; Table 7-iii). Therefore, contrast-enhanced images of fibrous plaques demonstrated a statistically significant change in attenuation with changing kVp (p = 0.001) while non-contrast enhanced images of these plaques did not. Comparison of contrast DEI values (densely-calcified: 0.052 ± 0.037; fibro-calcific: 0.031 ± 0.030; fibrous: 0.013 ± 0.020; lipid-rich [n = 3]: 0.006 ± 0.017) among plaque types yielded results similar to those using non-contrast DEI values: densely-calcified plaques were significantly different from fibrous and lipid-rich (overall type I error < 0.05, Tukey’s HSD test) plaques but no other pairwise comparisons reached statistical significance (Figure 7-4b).

Table 7-iii. Comparison of the attenuation of plaque types measured from contrast images at peak tube voltages of 80 kVp and 140 kVp.

<table>
<thead>
<tr>
<th>Pathology Type</th>
<th>Attenuation at 80 kVp (HU)</th>
<th>Attenuation at 140 kVp (HU)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Densely-calcified</td>
<td>738.8 (419.6)</td>
<td>551.2 (286.5)</td>
<td>187.6 (154.6)‡</td>
</tr>
<tr>
<td>Fibro-calcific</td>
<td>267.1 (182.8)</td>
<td>174.8 (110.9)</td>
<td>92.3 (85.9)§</td>
</tr>
<tr>
<td>Fibrous</td>
<td>79.6 (53.0)</td>
<td>51.9 (24.7)</td>
<td>27.7 (41.4)†</td>
</tr>
<tr>
<td>Lipid-rich</td>
<td>74.3 (68.8)</td>
<td>52.1 (46.4)</td>
<td>22.1 (50.0)</td>
</tr>
<tr>
<td>Lumen</td>
<td>272.4 (60.7)</td>
<td>171.1 (50.0)</td>
<td>101.4 (38.2) *</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation). Difference is the mean of pairwise differences.

* Statistically different from 0 at p < 0.001 according to sign test.
† Statistically different from 0 at p = 0.001 according to sign test.
‡ Statistically different from 0 at p = 0.001 according to sign test.
§ Statistically different from 0 at p = 0.012 according to sign test.
† Statistically different from 0 at p = 0.016 according to sign test.
7.5 Discussion

We examined the role of DECT for coronary plaque characterization by imaging human coronary arteries mounted in a previously validated, continuous pressure perfusion system. Analysis of non-contrast data from individual lesion sites at 80 and 140 kVp revealed significant differences in the attenuation of both densely-calcified and fibro-calcific plaque, but not of fibrous or lipid-rich plaques. Following contrast injection, plaque enhancement was demonstrated at both 80 and 140 kVp for all but lipid-rich plaque components. Analysis of data after contrast injection at 80 and 140 kVp demonstrated significant differences in the attenuation of fibrous plaques, in addition to densely-calcified and fibro-calcific plaques.

These data provide important insights into the potential role of CT for atherosclerotic plaque imaging. Previous single-energy CT studies demonstrated that only limited plaque characterization is possible as a result of the considerable overlap in HU values among different non-calcified plaque components (3-5, 18). These results reflect similar x-ray attenuation by the major components of non-calcified plaque using single-energy CT.

The use of DECT for coronary artery imaging is appealing because of the potential to provide additional attenuation data for plaque characterization. DECT exploits differences in x-ray interactions with tissue, mainly the photoelectric effect and Compton scatter (22, 23) which predominate at lower and higher x-ray energies, respectively. In addition, the photoelectric effect is more dependent on the atomic number of the material whereas Compton scatter is dependent on the physical density of the
material. Hence, with the use of two appropriate x-ray energies, materials can be differentiated based on their atomic number and physical density.

DECT has demonstrated the ability to discriminate between higher attenuating materials (calcium and iron) in phantoms (30). A major reason differences were not found in the current study, in particular in the attenuation of non-calcified plaques (fibrous and lipid-rich), is likely related to the composition of these plaque components. Within the diagnostic x-ray energy range, water composed largely of hydrogen (atomic number = 1, density =1 gm/cm³), shows no significant difference in attenuation with changing x-ray energy while materials such as calcium (atomic number = 20, density = 1.55 gm/cm³) and iodine (atomic number = 53, density = 4.94 gm/cm³) show large differences in attenuation (22, 23, 31). Non-calcified plaques vary in their composition from lipid to fibrous. However, at the molecular level these plaque components are quite similar and composed of elements with low atomic number. Even though tissue densities may vary, the differences may not be large enough to produce significantly different attenuations at the clinically available tube energy range used in this study. Hence, any differences in the HU values of non-calcified plaques at 80 and 140 kVp may be too small to be detected. However, in the current study, both calcium and iodinated contrast agent showed significant differences in attenuation across tube voltages. These results demonstrate the potential of DECT for separating calcium from contrast-enhanced lumen, currently a significant limitation for evaluation of the coronary arteries with single energy CT.

It is also important to note DECT techniques, like single energy CT techniques, are limited by the spatial resolution of clinical CT systems. The CT scanner used in this
study can at best resolve up to 0.4 mm x 0.4 mm. Plaque sizes vary from sub-millimeter to 3 mm or greater. Hence, the size of a lesion may be below the minimum spatial resolution of the scanner. Even when the plaque is of resolvable size, the number of pixels contributing to each measurement is small. As a result, noise can be high enough to distort the mean HU values even of larger non-calcified plaques preventing discrimination on the basis of attenuation.

Dual energy data can be acquired using either pre-reconstruction or post-reconstruction techniques (32). Pre-reconstruction techniques include scanning at two different x-ray energies consecutively or simultaneously. The results of this study are based on attenuation values acquired from consecutive single energy scans obtained at 80 and 140 kVp on a dual source scanner and are assumed to be equivalent to results from consecutive scanning at 80 and 140 kVp on a single source scanner. Simultaneous scanning can be accomplished using two x-ray sources, placing filters before the sample, or using energy selective detectors (32, 33). A cardiac (ECG –referenced) dual energy protocol that permits simultaneous data acquisition using two x-ray sources is now available on the dual source scanner used in this study. An advantage of simultaneous data acquisition, particularly for moving organs and vessels, is images acquired at different tube voltages are temporally registered (33). Because the ex-vivo model used in this study is stationary, temporal differences between consecutively acquired 80 and 140 kVp scans do not affect our data. As an extension of this study, additional data (three vessels with four lesions sites) were obtained using an optimized simultaneously acquired dual energy protocol (Figure 7-5). Although further evaluation of this protocol is
warranted, results are not expected to differ significantly from results with consecutively acquired single energy scans in a stationary model.

Contrast enhancement of atherosclerotic plaque has been observed in previous CT studies. Initial studies demonstrated that the presence of contrast agent in the lumen increases the mean attenuation of plaque within the vessel wall (2, 6, 7, 19). Further evaluation in perfusion models demonstrated active plaque enhancement after injection of iodinated contrast material in the vessel lumen (2, 6). The concept is supported by the results of our study, as fibrous plaque showed a significant difference in attenuation only in the presence of contrast agent (Table 7-iii) but no significant difference in attenuation in the absence of contrast (Table 7-i). Similarly, lipid-rich plaque showed almost no increase in attenuation with change in kVp in the absence of contrast (difference of 0.4 HU; Table 7-i) whereas in the presence of contrast an increase in attenuation was detected though it was not statistically significant (difference of 22 HU; Table 3). These HU differences for non-calcified plaque components found only in contrast scans are likely attributable to the differences in the attenuation of iodinated contrast agent in the plaque region rather than differences in the attenuation of plaque components. This finding may prove useful in the pursuit of plaque specific contrast agents (34, 35) for CT imaging.
Limitations of the current study include imaging of coronary arteries ex-vivo, matching CT images to histology, and a small sample size. Some degradation of the vessel structure at the cellular level cannot be avoided ex-vivo and the resulting impact on plaque attenuation is not completely known. The results of this study were also limited by the error in matching CT images to histology. Histology samples were obtained with a thickness of 5 μm while CT images were reconstructed with a thickness of 0.6 mm. In addition, CT images had to be reformatted orthogonal to the vessel axis to match the orientation of histology slides. Because the morphology of the plaque may vary significantly from CT to histology images, CT quadrants were matched to histology quadrants in an effort to improve the accuracy of the results (Figure 7-5). Finally, the current study was limited by a small sample size particularly in the category of lipid-rich plaques.

Ex-vivo imaging of coronary atherosclerotic arteries with DECT allows evaluation of this new technique for plaque characterization under ideal conditions. In this case, only densely-calcified and fibro-calcific plaques demonstrated a true change in
attenuation within the diagnostic x-ray energy range. Because the identification and classification of calcified and mixed-calcified plaques is often possible from CT images acquired at a single tube voltage (i.e., 120 kVp) (5), the added value of dual energy CT scans for the characterization of these plaque types has not been demonstrated. Additional attenuation data from non-calcified components would significantly improve characterization of these plaques, but based on the results of this study, such information does not appear to be available within the diagnostic x-ray energy range at the current spatial resolution of clinical CT scanners. However, given the small sample size for non-calcified plaques and other limitations of the study, additional investigation is warranted.

7.6 Conclusion

The potential application of DECT to the differentiation and classification of coronary artery plaques has been studied ex-vivo. Calcified plaques showed the largest difference in attenuation at 80 and 140 kVp and lipid-rich plaque (low atomic number and low density) showed the least. As a result, DEI values could only distinguish densely-calcified plaques from other plaque types. Further plaque discrimination was not possible due to an overlap in DEI values. Additional investigation using an expanded x-ray energy range and/or improved spatial resolution may yield different results.
7.7 References


CHAPTER VIII

LIMITS OF DUAL-ENERGY CT FOR CORONARY PLAQUE IMAGING: AN EX-VIVO STUDY USING MICRO-CT

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Specific aim 2: To explore the limits of clinically available x-ray based modalities for classification of atherosclerotic plaque.

The feasibility of using two different x-ray energies to separate plaque components is studied using micro-computed tomography (microCT). The higher spatial resolution and lower x-ray energies available with microCT compared to clinical CT are explored to understand the limitations of x-ray based imaging for plaque characterization.
The experimental methods, results and discussion based on the findings are included in this chapter.

8.1 Purpose

Current clinical computed tomography (CT) systems have limited ability to visualize and discriminate small low-density tissue such as coronary atherosclerotic plaque. Dual-energy CT (DECT) may have potential to improve both the visualization and discrimination of such tissue. However, in a previous study we demonstrated in an ex-vivo model that DECT offered no additional benefit for plaque characterization (1). MicroCT is a preclinical x-ray based modality that offers both higher spatial resolution (27 µm) and a lower range of x-ray energies (40 - 80 kVp) than clinical CT. Therefore, the limitations of clinical CT for plaque evaluation can be explored with respect to both engineering and physical principles using microCT. This study is designed to evaluate if clinical CT systems are limited in their ability to visualize low-density tissue by the available spatial resolution (0.4 mm³) or x-ray energy range (80 -140 kVp).

8.2 Methods

8.2.1 Tissue imaging

A segment of non-diseased human left descending coronary artery was excised at autopsy. The vessel was fixed and scanned in a 50 cc test tube filled with formalin. Prior
to scanning a radio opaque marker was placed on the tissue for matching the vessel to histology.

The vessel was scanned on a microCT scanner (Explore Locus, GE Healthcare, Milwaukee, WI) with three protocols using different x-ray tube voltages: 40 kVp, 60 kVp and 80 kVp. For a tube voltage of 40 kVp, the maximum available tube current (500 $\mu$A) was used to compensate for low penetration at this x-ray energy. For tube voltages of 60 and 80 kVp, tube currents were 400 $\mu$A and 150 $\mu$A, respectively. A calibration phantom containing water equivalent material, air bubble and calcium hydroxyapatite (CaHA) was also scanned along with the tissue.

Each slice was acquired with 360 projections/view with 2 frames averaged at every $1^\circ$ increment. Acquisition time for each view was 4 s. All data was acquired at an isotropic resolution of 27 $\mu$m. The time for each scan was around 45 minutes. A single volume was reconstructed from the acquired data using a Feldkamp cone beam kernel. Data from each scan were calibrated to classical CT attenuation values (Hounsfield units, HU) using water and air values from the calibration phantom. As a result, the CT number of water at each tube voltage was 0 HU. Attenuation in the vessel wall, fat surrounding the vessel and muscle was measured in images acquired at 40, 60 and 80 kVp. Measurements were made from circular ROIs placed in each tissue over 20 axial images along the length of the tissue. The ROIs were approximately 1100 pixels for fat, 70 pixels for vessel wall and 1050 pixels for muscle (Figure 8-1).

After imaging, the tissue was embedded in paraffin such that cross sections through the vessel were orthogonal to the vessel axis. Using a microtome, 5 $\mu$m thick sections were taken every 1 mm from the radio opaque marker. Histology sections were
stained with hematoxylin and eosin (H&E). Vessel wall thickness was measured in the histology images.

Figure 8-1. Axial image of the fixed coronary artery acquired using microCT at 40 kVp showing normal vessel wall (red), fat (blue arrow) and muscle (yellow arrow).

### 8.2.2 Statistical Analysis

To evaluate if any one tube voltage could sufficiently discriminate vessel wall, fat and muscle in the coronary tissue, mean attenuation values were compared for single tube voltages using one-way ANOVA and Tukey’s HSD test for multiple pairwise comparisons.
To assess whether the attenuation of tissue changes significantly with changes in tube energy, mean attenuation in each tissue type was compared across tube voltages. Further, possible improvement in tissue discrimination using two x-ray energies was evaluated by comparing differences in attenuation (attenuation at higher kVp subtracted from lower kVp) with tube voltage pairs (40/80 kVp and 60/80 kVp) using one-way ANOVA.

8.3 Results

The vessel wall was identified as normal from histology (Figure 8-2). The mean attenuation of fat, vessel wall and muscle was significantly different at all the x-ray tube voltages (one-way ANOVA, p<0.05) despite overlap for muscle and vessel wall for in each case (Table 8-i; Figure 8-3).

Figure 8-2. Histology image of normal vessel wall (black arrow) stained with H&E.
Table 8-i. Attenuation values of fat, vessel wall and muscle measured from images of coronary artery scanned with 40, 60 and 80 kVp using microCT.

<table>
<thead>
<tr>
<th>X-ray tube voltage (kVp)</th>
<th>Attenuation values (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fat</td>
</tr>
<tr>
<td>80</td>
<td>-188 ± 14.7</td>
</tr>
<tr>
<td></td>
<td>(-158, 219)</td>
</tr>
<tr>
<td>60</td>
<td>-206 ± 8.8</td>
</tr>
<tr>
<td></td>
<td>(-182, -219)</td>
</tr>
<tr>
<td>40</td>
<td>-289 ± 21.5</td>
</tr>
<tr>
<td></td>
<td>(-288, -313)</td>
</tr>
<tr>
<td>Difference (60/80)</td>
<td>-18 ± 10.7</td>
</tr>
<tr>
<td>Difference (40/80)</td>
<td>-100 ± 23.6</td>
</tr>
</tbody>
</table>

Figure 8-3. Attenuation of fat (black), vessel wall (red) and muscle (blue) at 40, 60 and 80 kVp.
The attenuation values were significantly different between 40 kVp and the higher energies (60 and 80 kVp) for all tissues. Comparison of attenuation between 60 kVp and 80 kVp revealed statistical differences in muscle alone.

The differences in attenuation at 40 and 80 kVp for, fat, muscle, and tissue were significantly different (p <0.05) indicating discrimination among the three tissues was possible combining data from these two energies. However, only fat could be separated from vessel wall and muscle (p<0.05) based on differences in attenuation of tissues at 60 and 80 kvp; muscle and vessel wall could not be separated.

8.4 Discussion

We observed that with the use of any 40, 60 and 80 kVp, the vessel wall could be discriminated from surrounding tissue (i.e. muscle and fat). However, the attenuation values overlapped for vessel wall and muscle at all energies, although to a lesser extent at 40 kVp (Figure 8-3). For each tissue, attenuation was significantly different at 40 and 80 kVp. Further, differences in attenuation between 40 and 80 kVp offered sufficient spectral separation to allow discrimination of vessel wall, muscle and fat in the ex-vivo coronary artery.

Normal vessel wall in the coronary arteries is around 0.35 mm thick (2). Even using the lowest energy available with clinical CT (80 kVp) vessel wall cannot be discriminated from fat or muscle in the heart without the presence of contrast agent in the lumen. One reason could be the limited spatial resolution (0.4 mm3 at best) of clinical CT scanners. At this resolution, small differences in vessel wall and fat or muscle attenuation
may not be appreciated. However, in this study, despite overlapping values, the vessel wall could be discriminated from surrounding tissue with the higher resolution microCT system at not only 40 kVp and 60 kvp but also 80 kVp. This indicates that improvement in the spatial resolution of clinical systems may provide more accurate measurement of attenuation values and allow visual discrimination of vessel wall, and possibly plaque components, from the surrounding tissue. However, quantitative evaluation may still be difficult with just one x-ray energy due to the overlap in attenuation values even at 40 kVp. A possible reason for the overlapping data with microCT could be the impact of noise in the images on attenuation measurements from the coronary vessel. High noise levels are inherent to microCT systems due to its very sensitive detector technology. Our protocols were adjusted during preliminary phantom studies to reduce noise. Averaging over two frames per projection reduced the image noise significantly yet noise in the images was still high: 459 HU at 40 kVp, 269 HU at 60 kVp and 318 HU at 80 kVp. Further reduction in image noise could be achieved by averaging over more than 2 frames but at the expense of significantly increased acquisition time.

The potential to discriminate between small low-density tissues using lower x-ray energies demonstrated in the current study supports previously reported findings (3). Langheinrich et al. showed that plaque components could be identified ex-vivo using microCT with 40 kVp and 8 μm resolution. Although, plaque discrimination may be possible using 40 kVp, human body imaging at such low energy may not be practical in-vivo due to limited x-ray penetration.

The number of photoelectric interactions of x-ray with matter increases with lower x-ray energies. As a consequence, increased tissue contrast is observed. However,
for tissues with similar atomic compositions, photoelectric interactions may not be sufficient to distinguish between tissues. Compton scatter on the other hand dominates at higher x-ray energies and is more sensitive to changes in the material density. Therefore, using a combination of low and high x-ray energies we may be able to exploit the different interactions in the materials to improve differentiation in tissues. We observed that the differences in attenuation with dual-energies were significant for all the three tissues only for the 40/80 kVp pair. This may be explained by the reduced overlap in attenuation values from vessel wall and muscle at 40 kVp, compared to attenuation at 60 and 80 kVp.

A limitation of this study is the tissue was fixed prior to imaging due to the long imaging time required for each protocol (~45 min per protocol) and the availability of the microCT system. Therefore, the attenuation characteristics may differ in comparison to fresh tissue. Also, the sample size was limited to one tissue due to extreme difficulty in attaining human coronary vessels.

8.5 Conclusion

Improving the spatial resolution alone in clinical CT scanners may improve visualization of small low-density tissue such as the vessel wall. However, quantitative discrimination of low density tissues still may not be possible at the lowest energy available with clinical CT (80 kVp) due to overlap in attenuation values. Further, lowering the x-ray energy range to 40 kVp for dual-energy acquisition could potentially allow for improvements in plaque discrimination.
8.6 References


CHAPTER IX

APPEARANCE OF CALCIUM IN VIRTUAL NON-CONTRAST (VNC) IMAGES
CREATED FROM DUAL-ENERGY CT DATA

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Engineering, Cleveland Clinic; § Siemens Medical Solutions, USA.

Specific aim 3: To separate calcium from iodine using dual-energy CT.

This aim is covered in the two chapters (VIII and IX). In this chapter, commercially
available software is evaluated creating VNC images and its effects on calcium volume.
The experimental methods, results and discussion based on the findings are described in
this chapter.
9.1 Purpose

The replacement of “true” non-contrast images with “virtual” non-contrast (VNC) images based on dual-energy three-material decomposition has recently been proposed for several clinical CT applications (1-5). Among the primary reasons for obtaining non-contrast images is the evaluation of calcium. However, calcium signal is reduced in VNC images since calcium is not one of the three basis materials used by the decomposition algorithm. The purpose of this study was to describe the appearance of calcium in VNC images created using manufacturer software (Syngo, Liver virtual non-contrast, Siemens) compared to “true” non-contrast images. Two methods of measuring the volumes were used: a semi-automated method and a manual method (used clinically).

9.2 Methods

9.2.1 Data acquisition

An anthropomorphic phantom containing 9 cylindrical calcifications of known sizes (length=diameter=1, 3 and 5 mm) and densities (200, 400 and 800 mg of CaHA per cc) (Figure 9-1) was scanned using a dual-source CT scanner (Siemens Definition). Scanning was performed with three phantoms simulating a small, medium and large thorax. Each phantom was imaged using a single energy protocol and a dual-energy protocol. A spiral mode of data acquisition was used for all scans. The single energy (SE) scans were performed with a tube voltage of 120 kVp, a reference tube current-time product of 270 mAs with anatomic-based modulation and collimated detector-row width
24 x 1.2 mm. Dual-energy (DE) scans were performed with peak tube voltages of 80 and 140 kVp and reference tube current-time products of 423 and 110mAs, respectively and a collimated detector-row width of 14 x 1.2 mm. Gantry rotation time was 500 ms for both protocols. Each phantom size was scanned five times with each protocol.

9.2.2 Virtual non-contrast Image creation

All images were reconstructed with 3 mm slice thickness using a medium-sharp kernel (B35f for SE and D30f for DE). Reconstruction of DE data resulted in two sets of images: 80 and 140 kVp. The two sets of DE images were used to generate VNC images using commercially available software (Syngo, Liver VNC, Siemens). Default parameter settings (range = 2, Relative contrast medium =2), defined by the manufacturer, were used. The range parameter controls the level of smoothing in the VNC image. Increasing the range increases the number of voxels included in the average. A second set of VNC images was created with range equal to 1 in order to assess the impact of the parameter on VNC creation.

9.2.3 Calcium measurements with semi-automated method

A semi-automated manufacturer software (Syngo, CaScoring, Siemens) was used to segment and quantify calcium. The calcium inserts were segmented using an attenuation based threshold. The threshold was adjusted to include all visible calcified inserts while excluding noise in the image that might be mistaken for calcium. Mean attenuation and volume were then measured for all inserts that were identified as
calcifications. Measurements from VNC range 1, VNC range 2 and SE image sets were compared.
Figure 9-1. Picture (Top) of calcium inserts in small thorax phantom. Schematic (bottom) of calcium phantom with 5 mm (large), 3 mm (medium) and 1 mm (small) inserts.
9.2.4 Calcium measurements using manual approach

A default cardiac window (window = 600 HU, level = 150 HU) was used to display the VNC images. Only VNC images created with range equal to 2 were used. Three measurements of diameter (d) were made from calcified inserts that were clearly visible. The diameter measurements were averaged and the volume of the insert was computed. Volume was calculated using the number of images for which the calcium insert was visible (n), the thickness of each image (3 mm) and the measured diameter:

\[ \text{volume} = \pi \left( \frac{d}{2} \right)^2 n \times 3. \]

9.2.5 Statistical Analysis

Measurements made using semi-automated methods from the calcium inserts in all 5 repetitions were grouped according to calcification size and density. To assess the effect of thorax size on calcium volume measurement from VNC images, volumes were compared across thorax size for VNC range 1, VNC range 2 and SE images. The mean differences in volumes were compared using one-way ANOVA and Tukey’s HSD test for multiple pairwise comparisons.

The effect of VNC creation on semi-automated volume measurement was assessed by comparing the three image sets obtained for a given thorax size. Again, the mean differences in volumes were compared using one-way ANOVA and Tukey’s HSD test for multiple pairwise comparisons.

Volumes measured from VNC images using the semi-automated and the manual methods were compared. The mean differences in volumes were compared using one-
way ANOVA and Tukey’s HSD test for multiple pairwise comparisons. For all measurements a p-value of 0.05 was considered statistically significant.

9.3 Results

9.3.1 Identification of calcified inserts

The CT number of calcium from VNC images was reduced by as much as 50% on VNC images compared to SE images (Figure 9-2). Large (5 mm) could be identified in all images except the 200 mg/cc density inserts, which could be identified in only 2/5 VNC image sets from the large phantom (Table 9-i). All 3 mm inserts were visible. 1 mm, 800 mg CaHA/cc inserts could be identified in only few SE (small thorax 2/5 repetitions, medium thorax 1/5 repetitions) and VNC (small thorax 3/5, large thorax 1/5). Therefore, no further comparisons were made from the 1 mm inserts.

9.3.2 Influence of Thorax size on measurement of calcium volume

No differences were observed in calcium volumes measured from SE scans of the three thorax phantoms with one exception. Only the volume of the 200 mg CaHA/cc, 3 mm insert was significantly smaller when imaged within the large phantom compared to both medium and small thorax phantoms (Table 9-i).
Figure 9-2. SE (top) and VNC [with range = 2] (bottom) image of the calcium phantom with small thorax. The appearance of small and low density inserts is diminished in the VNC image.
No differences were observed in calcium volumes measured from VNC scans of the three thorax phantoms except for the 400 mg CaHA/cc, 5 mm inserts measured from VNC range 1 in large and medium phantoms.

9.3.3 Influence of range parameter on measurements of calcium volume

Significant differences were observed in 5mm, 400 mg CaHA/cc inserts in the two VNC image sets from the small phantoms. No differences were seen all other in calcium volumes measured from VNC range 1 and VNC range 2 image sets.

9.3.4 Influence of VNC creation on measurements of calcium volume

1. A 5 mm, 800 mg of CaHA/cc insert: Calcium volumes from both VNC image sets were significantly different (overestimated) compared to volumes from SE images for all thorax phantoms.

2. 5 mm, 400 mg of CaHA/cc insert: Calcium volumes from both VNC image sets in small and medium thorax were significantly different (overestimated) compared to calcium volumes from SE images. However, no differences were observed between volumes measured from SE and VNC images in the large thorax.

3. 5 mm, 200 mg of CaHA/cc insert: No calcification was detected for the large phantom in both VNC image sets. Calcium volumes from VNC images with both ranges were significantly underestimated compared to SE volumes.
4. 3 mm, 800 mg of CaHA/cc: Significant differences (overestimation) were seen between volumes from VNC and SE images in small thorax. Also, volumes from images of medium thorax VNC Range 1 and SE images were significantly different.

5. 3 mm, 400 mg of CaHA/cc: No differences were observed in calcium volumes across image sets for all phantom sizes.

6. 3 mm, 200 mg of CaHA/cc: No calcium inserts were detected in both VNC image sets in the large phantom only. Calcium volume measured from both VNC images were significantly smaller compared to calcium volumes from SE images for medium and small phantoms.

Table 9-i. Volume measurements of calcium inserts in the phantom.

<table>
<thead>
<tr>
<th>Calcium volume measurements (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mm calcium insert</td>
</tr>
<tr>
<td>800 mg/cc</td>
</tr>
<tr>
<td>SE small thorax</td>
</tr>
<tr>
<td>SE medium thorax</td>
</tr>
<tr>
<td>SE large thx</td>
</tr>
<tr>
<td>VNC R2 small thorax</td>
</tr>
<tr>
<td>VNC R2 medium thorax</td>
</tr>
<tr>
<td>VNC R2 large thorax</td>
</tr>
<tr>
<td>VNC R1 small thorax</td>
</tr>
<tr>
<td>VNC R1 medium thorax</td>
</tr>
<tr>
<td>VNC R1 large thorax</td>
</tr>
</tbody>
</table>
9.3.5 Manual measurements of calcium volumes

Only 5 mm calcium inserts with 800 mg/cc CaHA could be seen in the VNC images clearly with the cardiac window. The volumes for small, medium and large thorax sizes were 192, 204, 207 cm\(^3\), respectively. Calcium volumes calculated from manually measuring the area in these inserts were significantly underestimated compared to semi-automated calcium volume measurements in VNC range 2 images.

9.4 Discussion

We observed three clear outcomes from the results: (1) High-density, non-iodine pixels loose intensity during VNC creation, (2) volume measurements of high density objects made manually from VNC images depend on the display window and level and, (3) contrary to visual perception, the volumes of these high-density objects can be larger in VNC than SE images, depending on their size.

Attenuation information from dual-energy images is used to create VNC images. The resultant grey values in the VNC image are not “true” Hounsfield values or CT numbers although the resultant VNC image is intended to provide attenuation values similar to a 120 kVp image. In fact we observed that low attenuating tissue did have the same intensity values in both SE and VNC images. However, the fidelity of calcium attenuation was lost in the VNC images. Calcium pixels lost as much as 50% of their intensity in VNC images as compared to SE images causing smaller calcifications to disappear. 200 mg/cc calcium insert were either not visible entirely or significantly smaller in the VNC images. This is because the algorithm for VNC uses three material
decomposition with fat, soft tissue and iodine as the basis materials (64). Calcium is not one of the materials used in the algorithm. Therefore, calcium or any other high attenuating materials are treated as a mixture of iodine and tissue, causing a loss in their pixel intensity during image processing.

Creating VNC images requires “super” smoothing of the dual-energy data and the degree of smoothing is defined by the range parameter. We observed in the high-density inserts that calcium appears larger in VNC compared to SE images. Although some difference is observed from range 2 to range 1 VNC images, the change in volume is not significant. This change would increase with increased smoothing (i.e., range >2) and could become significant, however.

The counter play of loss in pixel intensity and image smoothening becomes more evident in the 400 mg/cc inserts. We observed that the larger (5 mm) insert was overestimated however the medium (3 mm) insert was not significantly different in the volumes from VNC images.

Our third observation was that calcium volumes from VNC images were smaller when measured manually compared to the semi-automated measurements. In fact, with a cardiac display window and level, manual measurement yielded volumes smaller than the “true” (SE) volumes. However, semi-automatically measured volumes are in fact larger in VNC compared to SE images. In their study Takahashi et. al. observed that stones appeared smaller in VNC images as compared to “true” non-contrast images (4). Our results suggest that the appearance of smaller stones in VNC images can be due to either a loss in signal, which is more significant in low attenuation stones or the selected
window and level of the image display. Therefore, selection of the correct/appropriate window and level is critical for manual measurements of calcium from VNC images.

9.5 Conclusion

VNC images created using existing software can be used for qualitative assessment of high-density objects (coronary calcium, renal stones, stents etc). Though created specifically for evaluating the liver, the VNC software is an attractive tool for other applications (renal stones (4), coronary calcium quantification, aneurysms (2), etc.). However, quantitative measurements of volume, mass and/or density cannot be made reliably, as high intensity pixels are manipulated in VNC creation loosing their “true” intensity. Moreover, low-density calcifications may be lost entirely due to loss in pixel intensity making it appear like the surrounding tissue. Furthermore, manual measurement of volumes depends on the window and level of the display. Therefore, for quantitative evaluation from VNC images it has to be understood that in addition to iodine, both the intensity and size of high attenuating material or tissue will be affected by the VNC algorithm. This effect will be more pronounced in smaller and lower density objects.

9.6 References


CHAPTER X

CORONARY CALCIUM QUANTIFICATION FROM VIRTUAL NON-CONTRAST IMAGES CREATED USING CONTRAST-ENHANCED DUAL-ENERGY CT: AN EX-VIVO FEASIBILITY STUDY

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Specific aim 3: To separate calcium from iodine using dual-energy CT.

The potential for coronary calcium quantification from contrast-enhanced DECT images is investigated. An algorithm for calcium quantification was developed and implemented. This algorithm was validated against the clinical method currently used for
calcium scoring. The experimental methods, including details of the algorithm, results and discussion based on the findings are included in this chapter.

10.1 Abstract

Objective: To develop a robust method for separating calcium from iodine in contrast-enhanced dual-energy computed tomography (DECT) images and to create virtual non-contrast (VNC) images suitable for coronary calcium quantification.

Methods: This study was designated as exempt research by the institutional review board. Seven left anterior descending coronary arteries obtained at autopsy were scanned on a dual-source CT scanner. Each vessel was imaged with a conventional non-contrast (reference) and contrast-enhanced protocol (both using 120 kVp, 90 mAs/rot) and with a dual-energy contrast-enhanced protocol (Tube A: 80 kVp, 181mAs/rot; Tube B: 140 kVp, 45 mAs/rot). The two DECT image sets were initially processed to identify calcium. Using the resulting information and a dual-energy index for iodine (difference in attenuation divided by sum of attenuation at both tube voltages), iodine was removed from 140 kVp images to create VNC images. Calcium scores were then determined from reference, contrast-enhanced and VNC images.

Results: No significant differences were observed for volume scores (374±296 vs. 375±287 mm3) measured from VNC and reference images. However, volume scores (258±293 mm3) from single energy contrast-enhanced images were significantly lower than reference (p<0.02).
Conclusion: Reliable separation of luminal iodine and calcified plaque is possible in diseased human coronary arteries imaged ex-vivo with dual-energy CT permitting the creation of VNC images and the accurate determination of volume scores. Contrast-enhanced coronary DECT has the potential to provide both a description of luminal narrowing and prognostic information about calcium burden from a single acquisition.

10.2 Introduction

Coronary computed tomographic (CT) angiography is an accepted diagnostic test in defined symptomatic patient populations, and allows routine evaluation of the arterial lumen and vessel wall (1). In symptomatic patients, assessment of coronary anatomy has the immediate goal to exclude hemodynamically significant stenosis (typically defined as angiographic stenosis >50%), but also the longer-term goal to assess risk of future cardiovascular events. Based on post-mortem and imaging studies it is well known that plaque burden, measured by the calcium content, correlates with future events. Assessment of coronary calcification from non-contrast CT images (“calcium scoring”) is standardized and provides prognostic value complementary to description of luminal narrowing. However, quantification from contrast-enhanced CT images is limited because the attenuation values (measured in Hounsfield units) of calcium and iodine overlap (1-3).

The x-ray attenuation of a material depends not only on its density and composition but also on the energy of incident x-ray photons. Hence, two x-ray spectra generated at two different tube energies (dual energies) can be used to distinguish two
different materials. Theoretically, if applied to coronary CT angiography, dual-energy CT (DECT) has the potential to separate calcium from iodine (4, 5) in contrast-enhanced images and provide “virtual” non contrast images (VNC). Such VNC images derived from contrast-enhanced dual-energy images may be useful for quantifying coronary calcium.

The purpose of this study was to develop a method for separating calcium from iodine on contrast-enhanced DECT images and create VNC images suitable for calcium quantification. Data were obtained for this purpose from excised atherosclerotic human coronary arteries obtained post-mortem.

10.3 Materials and Methods

10.3.1 Vessel preparation

This study was designated as exempt research by the local institutional review board. Seven left anterior descending (LAD) coronary arteries along with some surrounding tissue were excised from humans, post-mortem. All vessels were imaged and fixed within 48 hours of autopsy and refrigerated at all times except during imaging. Before imaging, the coronary ostium was cannulated and the proximal end of the vessel was secured on a wax base. The vessel was then continuously perfused with saline using a pressurized (100 – 140 mmHg) perfusion system, which also permitted injection of contrast agent (6).
10.3.2 Scan protocol

All scanning was performed on a dual-source multi-detector row CT scanner (Definition, Siemens Healthcare, Forchheim, Germany). Each vessel was scanned with a single energy non-contrast protocol (reference), a single energy contrast-enhanced protocol, and a dual-energy contrast-enhanced protocol. A spiral mode of acquisition was used for all scans and reconstruction was synchronized to a simulated ECG signal. Contrast agent was injected into the saline stream, when needed, using an automated contrast injector (Stellant D, Medrad Inc., Indianola, PA). The flow rate and concentration of contrast agent were adjusted to match clinically relevant attenuation of contrast-enhanced blood in the lumen (250 – 350 HU at 120 kVp).

For dual-energy scans the widest spectral separation available on the scanner was selected. Each tube was operated independently: tube A at 140 kVp and tube B at 80 kVp. To achieve minimum image noise, the tube current-time product for tube B (80 kVp) was set to the maximum value of 181 mAs/rotation. For dual-energy post-processing purposes, current across Tube A was adjusted to achieve equivalent noise with both tubes; a tube current-time product of 45 mAs/rotation was selected for Tube A based on water phantom scans to provide equivalent noise. For single energy scans, both tubes were operated at a voltage of 120 kVp and a current-time product of 90 mAs/rotation. Again, water phantom scans were used to determine the tube current necessary for single energy images to match the noise level of DECT images. The tube current was kept constant during the simulated cardiac cycle for all scans.

Except for tube voltage and tube current-time product all acquisition and reconstruction parameters were identical for single and dual-energy scans. Data were
acquired using 32 x 0.6 mm detector row collimation with double z-sampling and 0.33 s gantry rotation time. Images were reconstructed with 200 x 200 mm$^2$ field-of-view, 0.6 mm slice thickness with 0.3 mm slice increment, and a medium-smooth reconstruction kernel (B35f) recommended for calcium quantification. The dual-energy data were reconstructed as two separate image sets (80 and 140 kVp), which were used to create VNC images. Single energy images were not processed further.

### 10.3.3 Virtual Non-contrast Image Creation

VNC images were created from contrast-enhanced DECT images in two separate steps: 1) calcium identification and 2) iodine removal (Figure 10-1). Calcium was identified on DECT images with commercially available software (Syngo, Dual Energy Bone Removal, Siemens) that uses three-material decomposition to discriminate iodine-blood mixtures from bone (7). A ratio defines the slope of the line bisector used to differentiate iodine from bone in an 80 versus 140 kVp plot. The default ratio, 1.75, was used in this study. The regions identified as calcified were removed and the resulting images were exported offline and used to create a mask to exclude calcium from subsequent image processing (Figure 10-1).

Iodine removal was performed in a separate step using custom software created with a commercial programming tool (Matlab, The Mathworks, Inc., Boston, USA). The calcium mask created in the first step was applied to the higher energy (140 kVp) contrast-enhanced images. A DE$_{\text{Index}}$ was computed for all pixels using attenuation values (in HU) averaged over a 3 x 3 matrix (centered on each pixel) from 80 kVp (x80) and 140 kVp (x140) images: $\text{DEIndex} = (x_{80} + x_{140}) / (x_{80} + x_{140})$. All pixels with a DEindex
value corresponding to iodine (range: 0.15-0.4) were subtracted from the unmasked regions of the 140 kVp images. The resultant unmasked VNC images, then, were essentially 140 kVp images with iodine removed.
Figure 10-1. Method of calcium quantification from “true” and virtual non-contrast images. Conventionally, calcium is quantified from segmented, non-contrast images. Using dual-energy CT, virtual non-contrast images are created from contrast-enhanced 80 and 140 kVp images acquired simultaneously. Calcium is quantified from VNC images using the same segmentation method as in “true” non-contrast images.
10.3.4 Calcium Quantification

Three sets of images from each vessel were analyzed: non-contrast 120 kVp (reference images), contrast-enhanced 120 kVp and VNC 140 kVp images. Calcium volume and mass scores (8) were determined from all image sets using commercially available software (CaScoring, Siemens Healthcare, Forchheim, Germany).

Calcified lesions were identified on all CT images prior to calcium scoring by applying an attenuation or density threshold. A density threshold of 100 mg/cm$^3$ CaHA (9) was used to segment calcium from both the reference images and VNC images. For contrast-enhanced images, an adapted attenuation threshold calculated as the mean attenuation (HU) of contrast agent in the vessel lumen plus twice the standard deviation (mean + 2*SD) was used (10).

Calcium was quantified independently by two experienced readers (10 and more years of experience in cardiac CT), blinded to the data acquisition and image processing techniques. Due to the nature of the ex-vivo setup, high attenuating pixels arose from metal clips, pins and iodine that lay on and around the tissue. These were deliberately ignored and only high attenuating pixels within the tissue were counted as calcium. When the origin of high attenuating pixels was in doubt, a consensus reading was reached.

The volume score for each lesion was estimated as the product of the number of voxels containing calcium and the volume of one voxel; the scores for all lesions in a given coronary artery were summed to obtain the total volume score. The calcium mass score was calculated for each lesion as the product of a calibration factor, the volume of the lesion, and the mean attenuation of the lesion. The calibration factor was set to a scanner and tube voltage specific value determined by the manufacturer: 0.776
mg/(HU*cm³) for 120 kVp (reference and contrast-enhanced) and 0.867 mg/(HU*cm³) for 140 kVp (VNC) images. The mean attenuation, or mean CT number, of each lesion was automatically computed by the calcium scoring software. Again, the total mass score for a given coronary artery was the sum of the scores for all lesions. Finally, using the volume and mass scores output by the scanner software, as well as the appropriate calibration factor, the CT number for calcium was determined per vessel.

10.3.5 Statistical Analysis

Agreement between the two readers for calcium scoring was analyzed separately for each protocol. The Wilcoxon signed-rank test was used to assess whether there was statistical evidence that one reader’s measurements tended to be higher than the other.

To evaluate the agreement in quantifying calcium from contrast-enhanced images and reference images, calcium scores were compared using nonparametric analysis (Wilcoxon signed-rank test). Similar analysis was performed to evaluate agreement between VNC and reference images. The effect of iodinated contrast agent in the lumen on calcified plaque was observed by comparing the mean attenuation of calcium from both the non-contrast and contrast-enhanced images (Wilcoxon signed-rank test). For all analysis a p-value of less than 0.05 was considered significant.

10.4 Results

VNC images were successfully created from contrast-enhanced dual-energy images (Figure 10-2) for all seven vessels. Sixty-two calcified lesions were identified by
reader 1 while 66 were identified by reader 2. Consensus reading was needed for evaluation of VNC images from one vessel. No significant differences between the two readers were found for calcium scores (Table 10-i, Table 10-ii).

![Figure 10-2. Cross-section of ex-vivo coronary artery at the location of a calcified lesion.](image)

Contrast-enhanced 120 kVp image (a), simultaneously acquired, contrast-enhanced 80 kVp (b) and 140 kVp (c) images, “true” non-contrast at 120 kVp image (reference) (d), virtual non-contrast 140 kVp image created from contrast-enhanced 80 and 140 kVp images (e) and illustration of luminal area (red) and calcified area (white) (f).
10.4.1 Volume Scores

No significant differences in calcium volumes were observed between reference and VNC images (Table 1, Figure 3). However, volume scores derived from contrast-enhanced 120 kVp images were significantly less than those derived from reference images \((p = 0.016, \text{ Wilcoxon signed-rank test, } \text{Table 10-i, Figure 10-3})\) with underestimation of volume scores in all vessels (Figure 10-3). The mean differences between volumes measured from contrast-enhanced and reference images were \(-89 \text{ mm}^3\) for reader 1 and \(-95 \text{ mm}^3\) for reader 2, ranging between \(-202 \text{ and } -17 \text{ mm}^3\) for both readers.

![Figure 10-3. Calcium volume scores measured from contrast-enhanced 120 kVp (diamond) and virtual non-contrast (VNC) (square) versus reference measurements according to reader one. Straight line denotes perfect agreement. Volumes from VNC](image-url)
images are not significantly different from reference images. All volume scores from contrast-enhanced images are underestimated compared to scores from reference images.

Table 10-i. Volume Scores

<table>
<thead>
<tr>
<th>Volume (mm³)</th>
<th>“True” Non-contrast</th>
<th>“Virtual” Non-contrast</th>
<th>Contrast-enhanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>347 ± 296*</td>
<td>375 ± 287</td>
<td>258 ± 293*</td>
</tr>
<tr>
<td>Reader 2</td>
<td>354 ± 299#</td>
<td>379 ± 284</td>
<td>259 ± 287#</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation. “Virtual” non-contrast images are derived from contrast-enhanced dual energy images.

* Statistically different from 0 at p<0.02 according to Wilcoxon signed-rank test
# Statistically different from 0 at p<0.02 according to Wilcoxon signed-rank test

10.4.2 Mass scores

Unlike volume scores, measurements of mass scores from VNC and reference images showed significant differences (p = 0.016, Wilcoxon signed-rank test; Table 10-ii; Figure 10-4). The mean differences between mass scores measured from VNC and reference images were 24 mg of CaHA for reader 1 and 23 mg of CaHA for reader 2, ranging between 7 and 62 mg of CaHA for both readers. However, mass scores from contrast-enhanced images compared to reference images were not significantly different (Table 10-ii; Figure 10-4).
Table 10-ii. Mass Scores

<table>
<thead>
<tr>
<th></th>
<th>“True” Non-contrast</th>
<th>“Virtual” Non-contrast</th>
<th>Contrast-enhanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>134±141*</td>
<td>158±150*</td>
<td>147±173</td>
</tr>
<tr>
<td>Reader 2</td>
<td>137±142#</td>
<td>160±149#</td>
<td>149±170</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation. “Virtual” non-contrast images are derived from contrast-enhanced dual energy images.

* Statistically different from 0 at p<0.02 according to Wilcoxon signed-rank test

# Statistically different from 0 at p<0.02 according to Wilcoxon signed-rank test
Figure 10-4. Calcium mass scores from contrast-enhanced 120 kVp (diamond) and virtual non-contrast (VNC) (square) versus reference scores according to reader one. Straight line denotes perfect agreement. Mass scores from VNC images are overestimated compared to scores from reference images likely due to the increase in calcium attenuation with the presence of iodine in the lumen.

### 10.4.3 Calcium Attenuation

Mean calcium CT numbers were not significantly different for reference and VNC images despite the higher tube voltage (and, therefore, expected reduction in calcium CT number) for VNC images. Yet, calcium CT numbers were significantly higher for contrast-enhanced compared to reference images (Wilcoxon signed-rank test, \( p = 0.016 \), Table 10-iii) even though both image sets were acquired at 120 kVp. The mean
differences between CT numbers measured from contrast-enhanced and reference images were 322 HU (range: 186 – 538 HU) for reader 1 and 323 HU (range: 186 – 524 HU) for reader 2.

Table 10-iii. Calcium attenuation

<table>
<thead>
<tr>
<th>Attenuation (HU)</th>
<th>“True” Non-contrast</th>
<th>“Virtual” Non-contrast</th>
<th>Non-contrast</th>
<th>Contrast-enhanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>440 (211-631) *</td>
<td>440 (239-611)</td>
<td>762 (580-1087)*</td>
<td></td>
</tr>
<tr>
<td>Reader 2</td>
<td>441 (211-622) #</td>
<td>442 (239-611)</td>
<td>765 (580-1073)#</td>
<td></td>
</tr>
</tbody>
</table>

* Statistically different from 0 at p<0.02 according to Wilcoxon signed-rank test  
# Statistically different from 0 at p<0.02 according to Wilcoxon signed-rank test

10.5 Discussion

A post-processing method was developed allowing the accurate determination of volume scores from contrast-enhanced dual-energy CT data of human coronary arteries imaged ex-vivo. Reliable separation of luminal iodine and calcified plaque in dual-energy images permitted the generation of VNC images. Analysis of VNC images revealed accurate quantification of calcium volume but not calcium mass. Agatston scores were not determined from ex-vivo coronary images since the comparison of scores would not be valid across tube voltages (i.e., 120 kVp reference images vs. 140 kVp VNC images) without significant adjustment (11).

Quantification of coronary calcium from contrast-enhanced CT studies is a topic of great interest. Reliable calcium quantification would yield prognostic information from
coronary CT angiography beyond luminal narrowing. Previous studies have attempted to quantify calcium from single-energy contrast-enhanced CT images by adjusting threshold settings to prevent contrast agent in the lumen from being counted as calcium. In the current study, contrast-enhanced single energy scans were scored using a threshold adjusted to scan-specific luminal enhancement (mean + 2*SD). Volume scores derived from the contrast-enhanced 120 kVp images were significantly lower than reference scores suggesting some calcium was removed with iodine during segmentation.

Determination of mass scores from contrast-enhanced images is further dependent on the enhancement of plaque. The presence of contrast in the lumen has been observed to significantly increase measured plaque attenuation, including calcified plaque (6, 12, 13). This could lead to an artificial increase in mass scores if the change in mean calcium CT number is large enough.

In the current study, the mean CT number for calcium was significantly higher measured from contrast-enhanced compared to non-contrast reference images despite acquisition of both images sets at 120 kVp. This had a significant impact on mass scores. Because volume scores were underestimated from contrast-enhanced 120 kVp images compared to reference non-contrast 120 kVp images, multiplication of the former values with a larger mean CT number but the same calibration factor compared to the later resulted in equivalent mass scores.

Through additional analysis not presented here in detail, we found the use of a lower segmentation threshold just one standard deviation above the mean luminal attenuation (mean + SD) yielded the same results. Therefore, previous studies (2, 3, 14) as well as the current study indicate that calcium quantification is not reliable from
contrast-enhanced single energy CT images by simply adjusting the threshold to isolate calcium.

It has been reported that differences in attenuation at 80 and 140 kVp are significant for both calcium and iodine (6). The separation of calcium and iodine using DECT has been demonstrated in phantoms (15, 16) and non-cardiac ex-vivo specimens (4, 5, 17). However, to our knowledge, the generation of “virtual” non-contrast images from contrast-enhanced DECT images for the purpose of coronary calcium scoring has not been investigated. The VNC images created in this study were essentially 140 kVp images with iodine removed and, therefore, could be used for calcium evaluation by simply adjusting the threshold and, in the case of mass scoring, the calibration factor, to that typically used for 140 kVp.

Quantification of coronary calcium from VNC images derived from contrast-enhanced dual-energy images presents fewer obstacles than quantification from contrast-enhanced single energy images due to improved separation of calcium and iodine. In fact, separation was sufficient in the current study to create VNC images that yielded volume scores equivalent to those from reference images. However, mean CT numbers in the VNC images were still elevated due to the presence of contrast during data acquisition. Because VNC images represent data acquired at 140 kVp while reference images provide data acquired at 120 kVp, decreased attenuation of calcium and, subsequently, lower CT numbers for calcium would be expected in the higher energy VNC images. Yet, the attenuation of calcium was similar on VNC and reference images suggesting calcified plaque enhancement during contrast-enhanced DECT data
acquisition. Again, these artificially elevated CT numbers impacted mass scores. Mass scores were significantly higher from VNC compared to reference images.

![Image](image1.jpg)

Figure 10-5. “False” calcified lesion (arrow) appearing in virtual non-contrast image (a) due to incomplete removal of iodine. Calcified lesion is not seen in “true” non-contrast image (b).

**Limitations**

The ex-vivo setup used for this study was unable to fully address some factors critical for in-vivo DECT imaging including excessive noise, radiation dose and cardiac motion. In this study, Tube B was operated at maximum power to minimize image noise. Yet, the appearance of false “calcifications” was still noted in ex-vivo images in part because of misidentification of noisy pixels as calcium (Figure 10-5). Obviously, noise will increase in-vivo due to the presence of more attenuating tissue around the heart. However, it is expected that 3 mm thick VNC images (clinical standard for calcium scoring) would be reconstructed clinically for the purpose of calcium quantification rather than the 0.6 mm thick images analyzed in this study serving to lower noise and potentially reduce occurrence of false calcifications. The appearance of false
calcifications may also be explained by the dependence of the calcium-iodine bisector on spectral separation (15). Significant overlap of the low and high energy spectra occurs with the first generation dual-source CT scanner used in this study. However, improved spectral separation has been achieved with newer dual-source CT systems using an energy selective filter to remove the lowest energy photons from the high energy (e.g. 140 kVp) spectrum (18). In addition to improving calcium-iodine separation, filtration of the high energy spectra may allow the use of 100 kVp for generation of the low-energy spectrum, which would serve to reduce image noise (15). Although further from clinical realization, the use of photon counting detectors (19) should also yield greater separation of low and high energy spectra and may improve the identification of calcium on contrast-enhanced images (15, 20).

Care was not taken to minimize dose with DECT protocols used in this ex-vivo study. However, dose values reported for dual-energy protocols used for in-vivo coronary CT imaging were similar to single energy protocols (21, 22). For the dual tube system used in these studies, reduced DECT radiation dose may even be possible with the addition of the energy selective filter referenced above (18). Also, no dose penalty is expected for dual compared to single energy imaging using dual-layer detector technology (17).

Finally, the affects of motion were not studied here but will have an impact in-vivo. That impact may depend on the method of DECT data acquisition. The scanner used in this study employs two sources placed orthogonally to acquire DECT data which may be more challenging for temporal matching as compared to alternating tube energies (23) or dual-layer detector acquisition (17).
10.6 Conclusion

We demonstrated reliable separation of luminal iodine and calcified plaque in ex-vivo human coronary arteries imaged with contrast-enhanced dual-energy CT using a novel post-processing method to create “virtual” non-contrast images. This technique allowed accurate determination of Agatston and volume scores from VNC images. Quantification of calcium mass was hindered by the enhancement of calcified plaque during the injection of iodinated contrast. Still the potential exists for extracting both a description of luminal narrowing and prognostic information about the extent of calcium burden from a single, contrast-enhanced coronary DECT scan.

10.7 References


CHAPTER XI

CONCLUSION

Over the last decade CT technology has advanced rapidly, especially for cardiac applications. Coronary CT angiography is now an accepted clinical tool for diagnosis of coronary artery disease. Except for ionizing radiation, coronary CT offers a non-invasive method for evaluating calcified and non-calcified plaque and has a higher accuracy for detecting stenosis based on comparison to conventional invasive angiography. Also, if used according to established guidelines, coronary CT angiography can be more accurate and cost effective compared to a conventional diagnostic workup (electrocardiogram, echocardiography, stress tests, blood tests) (74).

The aim of this research was to evaluate the feasibility of using dual-energy CT for the purpose of plaque discrimination and quantification. As described in chapter VI, coronary arteries excised from humans ex-vivo were scanned using two tube energies. The plaque was then identified according to histology. The measured plaque attenuation at the different tube voltages was then compared for each plaque type. Plaque could be distinguished as calcified and non-calcified. However, non-calcified plaque could not be
further discriminated as fibrous or lipid based on the differences in attenuation between two tube voltages. However, it was observed that DECT did allow discrimination of calcified plaque and iodine (contrast agent). The lack of observed differences in attenuation of non-calcified plaque components could be due to similarities in the composition of non-calcified plaques, the spatial resolution of the CT scanner or the tube voltages used in the study.

The scanner at best has 0.4 mm isotropic resolution, which is comparable to the plaque sizes and therefore, may not have sufficient pixels to reliably resolve the plaque. This is supported by the microCT results, which showed that with isotropic resolution of 27 \( \mu \)m, non-diseased vessel wall (measuring approximately 0.2 mm) could be discriminated from the surrounding tissue even at a single energy (80 kVp). Future developments in scanner hardware and software may allow improvements in spatial resolution sufficient to permit discrimination of non-calcified plaque.

The composition of non-calcified plaque components is similar. Therefore, only small differences in attenuation between fibrous and lipidic plaques exist at the energies currently available on commercial CT systems. However, attenuation differences would be magnified if the x-ray spectra offered predominantly photoelectric interactions. Lowering the tube voltage increases photoelectric interactions and may improve attenuation-based plaque discrimination with DECT, which is supported by the microCT results. However, x-rays produced with lower tube voltage may not have sufficient energy to penetrate the body. Further, the tube voltages used in this study (80 and 140 kVp), the widest range of voltages available on commercial CT scanners, show an overlap in the x-ray spectra generated (Figure 11-1). Adding a filter to the high-energy
tube increases the spectral separation (75) and may amplify differences in attenuation of non-calcified plaque.

The scanner technology required that all dual energy analysis be done post-reconstruction. Therefore, some of the low frequency data essential for plaque discrimination may have been lost.

Figure 11-1 Relative energy detected from each tube at 80 kVp (blue) and 140 kVp (red) for Siemens Definition scanner. The detected spectra have little separation in the two energies. Added filtration to the 140 kVp tube (dark red) shows more separation in detected energy spectra [75].

Following the results in chapter VI, DECT was used to separate iodine from calcium in ex-vivo coronary images. Iodine was successfully removed from the contrast-enhanced images and “virtual” non-contrast images were created. Calcium was then
quantified from the virtual non-contrast images using commercially available quantification software. Results showed that only calcium volumes were accurately measured when compared to volumes from true non-contrast images. However, calcium mass was significantly higher in the VNC images. This finding was attributed to the uptake of contrast agent by the calcified plaque, which makes calcified plaque appear denser. From these results, there is potential use for DECT to separate calcium from iodine in a clinical setting. Further, calcium can be quantified from VNC images created using DECT. However, mass scores will have to be adjusted for iodine uptake.

The work presented in this dissertation has raised some research questions that should be addressed in the future.

1. Will the anticipated improvements in spatial resolution with commercial CT scanners allow coronary artery plaque discrimination? This could be explored using microCT for imaging coronary plaque in an ex-vivo human or phantom model. The x-ray spectra generated by a microCT system can be different from a clinical CT system and might have to be accounted for. However, if using the highest available tube voltage in a microCT system shows differences in plaque, a similar trend can be expected from a clinical CT system with the same resolution.

2. Can alternative DECT techniques, such as dual-layered detectors and alternating tube energies, improve plaque discrimination? The use of an alternative dual-energy technique may allow analysis of attenuation data prior to reconstruction and hence, offer access to low frequency data that is essentially filtered during reconstruction.
3. Is the uptake of contrast agent linear? The calcium mass scores from VNC images appeared to have a linear change in the enhancement compared to calcium mass scores from true non-contrast images. This may provide a means of adjusting for the differences in the mass scores observed in the VNC images due to the enhancement of calcified plaque. This question can be explored in an ex-vivo setting where the same vessel is scanned repeatedly while increasing the concentration of contrast agent. However, we do not know if the contrast uptake in plaque is due to physiological break down of the tissue ex-vivo. Therefore, the most accurate data will be acquired from patient studies.

4. Can the amount of contrast agent uptake be used to identify the type of plaque? This research question is of great interest, especially for the development of targeted contrast agents. An ex-vivo design with peripheral arteries where the dimensions of plaque is larger than coronary arteries could be used with clinical CT. Also, microCT could be used to accurately identify the plaque type ex-vivo and quantify the contrast uptake.

5. Is there potential use of DECT for measuring non-calcified plaque burden? In this study, VNC images were created only from densely calcified vessels. The same method can be used for diseased vessel with all types of plaque and a mathematical model could be developed using the contrast uptake by plaque delineate the plaque.
6. Can the segmentation of calcium from surrounding tissue be attenuation independent? Segmenting calcium from the surrounding tissue is accomplished using an attenuation threshold. This makes the segmentation highly dependent on the threshold value and the resulting volumes could be inaccurate. Applying a segmentation method that uses the intensity profile or the histogram of the images may provide a segmentation method that is not dependent on the attenuation of the pixels but the contrast between the calcium and the surrounding tissue.

In conclusion, this research has shown that DECT using commercially available systems has the potential to quantify calcium from contrast-enhanced images but is still limited in its ability to discriminate non-calcified plaques. Better spectral separation and improved resolution in clinical CT systems may allow plaque discrimination.
REFERENCES

Reference for Chapters I-VI and XI


53. Leber A, Knez A, Becker A, Becker C, Boekstegers P. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of


References for Chapter VII


References for Chapter VIII


References for Chapter IX


References Chapter X


APPENDIX
Appendix A

PROGRAM FOR CREATING VIRTUAL NON-CONTRAST IMAGES WRITTEN IN MATLAB

% Program name: seimensVNC
% Main function to create "Virtual" Non-Contrast images from 80 and 140 kVp images. This program uses images from Siemens bone removal software to create a Calcium mask.
%
% LOGIC
% This program requires three sets of images as inputs; original 140 kVp, original 80 kVp and the suppressed calcium images. The suppresses calcium images are used to create a calcium mask by using the suppressed images as a negative.
%
% -- Mitya Barreto Jan 20th 2009

CELL 1: INITIALIZE FOLDERS

% INITIALIZE THE FOLDERS CONTAINING 140, 80 AND SUPPRESSED CALCIUM IMAGES
%

USER VARIABLES

path140, path80, pathSuppressed: paths to 140, 80 and suppressed Images
files140, files80, filesSuppressed: Cells containg the names of respective files
[path140, files140] = getPath('C:\', 'Enter the path to 140 kVp images');
[path80, files80] = getPath(path140, 'Enter the path to 80 kVp images');
[pathSuppressed, filesSuppressed] = getPath(path140, 'Enter the path to suppressed ... images');

% MAKE A FOLDER TO SAVE THE VNC IMAGES. IN THIS CASE
% THE VNC IMAGES WILL BE SAVED IN A FOLDER CALLED
% VNC_siemens WITHIN THE 140 kVp FOLDER
if ~exist([path140 '\VNC_siemens'], 'dir')
    mkdir([path140 '\VNC_siemens']);
end

% INITIALIZE THE COUNTERS
maxCount = max(size(files140(:))); % number of images in the data set
i = 1:512; j = 1:512; % Counters for rows (i) and columns (j)

CELL 2: CREATE VNC

% THE MAIN LOOP
% READ IMAGES INDIVIDUALLY AND CREATE VNC
for count = 1 : maxCount
    dicom140 = double(dicomread([path140 '\ files140{count}])-1024;
    dicom80 = double(dicomread([path80 '\ files80{count}])-1024;
if count == 1
    figure(1); imshow(dicom140, [-200 400]); title(['Original 140 kVp image' …
    num2str(count)]);
end

% COMPUTE DEI VALUES USING ORIGINAL DUAL-ENERGY IMAGES
% SI: MATRIX WITH DEI VALUES FROM ENTIRE IMAGE
% SI_I: LOGICAL MATRIX WITH DEI VALUES FOR IODINE ONLY
SI = computeDEI(dicom140, dicom80);
SI_I = ((SI(i,j)>=0.05)& (SI(i,j)<=0.4) & (dicom80 > 100));

% CREATE THE CALCIUM MASK FROM THE SUPPRESSED IMAGES
% imageNumber: TEMPORARY IMAGE COUNTER.
% imageSuppressed: MATRIX CONTAINING THE SUPPRESSED CALCIUM
% IMAGE
% NOTE: The suppressed images may be numbered in opposite direction to
% the original dual-energy images.
% If Orientation is opposite to original data
imageNumber = maxCount -(count-1);
% else comment above statement and use the next statement.
% imageNumber = count;
imageSuppressed = dicomread([pathSuppressed ' 

filesSuppressed{imageNumber}]);

% RANDOM CHECK POINT
if count == 1
    figure(2); imshow(double(imageSuppressed)-1024, [-200 400]);
    title(["Suppressed image' num2str(imageNumber)]);
    wait= input('next iteration?');
end

% CONVERT CALCIUM IMAGE FROM DOUBLE TO BINARY.
% THIS MAP HAS CALCIUM VALUE AS ZERO.
BWsuppressed = logical(imageSuppressed);

% FIND 3-DIMENSIONAL CONNECTIVITY AND REMOVE ALL
% REGIONS WITH LESS THAN  8-CONNECTIVITY
% BWsuppressed: TEMPORARY 3-D MATRIX WITH 3 IMAGES
% FOR CONNECTIVITY
% CaMask: CONTAINS THE 8-CONNECTED NEGATIVE OF THE
% CALCIUM MASK
if imageNumber == 1
    imageSuppressed1 = zeros(512,512);
else
    imageSuppressed1 = dicomread([pathSuppressed '\ ...
filesSuppressed{imageNumber-1}]);
end

if imageNumber == maxCount
    imageSuppressed3 = zeros(512,512);
else
    imageSuppressed3 = dicomread([pathSuppressed '\ ...
filesSuppressed{imageNumber+1}]);
end

BWsuppressed(:,:,1) = logical(imageSuppressed1);
BWsuppressed(:,:,2) = logical(imageSuppressed);
BWsuppressed(:,:,3) = logical(imageSuppressed3);

CaMask = minConnect(BWsuppressed);

clear BWsuppressed imageSuppressed1 imageSuppressed...
imageSuppressed3;

% CREATE THE CALCIUM MASK
% CaOnly: CALCIUM MASK WITH 8-CONNECTIVITY
CaOnly = not(CaMask(i,j,2));

clear SI imageSuppressed;

% CREATE AN IODINE MATRIX EXCLUDING CALCIUM
% I: IODINE ONLY MATRIX
I = SI_I & (not(CaOnly));
clear SI_I CaOnly;

% VNC: FINAL VNC IMAGE!
VNC = uint16(((dicom140 & not(I)).*dicom140) +1024);

% USE META DATA FROM 140 kVp IMAGES FOR VNC
% METADATA
% metaInfo: STRUCTURE CONTAINING THE META DATA
metaInfo = dicominfo([path140 '\ files140{count}]);
% WRITE THE VNC IMAGE; MAKE SURE TO COPY THE
% PRIVATE FIELDS IN THE METADATA
dicomwrite(VNC, [path140 '\VNC_siemens\' files140{count}], …
metaInfo, 'CreateMode', 'Copy', 'WritePrivate', 'True');
close all;

ends
function CaMask = minConnect(BWsuppressed)

% FUNCTION: minConnect
% checks for minimum connectivity in the calcium mask
% requires the input from the suppressed calcium images.
% returns the 8-connected calcium mask.

CaMask = BWsuppressed;
[L, num] = bwlabeln(not(BWsuppressed));
for i = 1: num-2
    [row, col,tempSize] = find(L==i);
    if length(tempSize) <=20
        CaMask(row,col)=1;
    end
end

function DEIval = computeDEI(dicomImage140, dicomImage80)

% FUNCTION: DEIval
% computes the DEI values from two dicom Image sets
% Requires the input from dual-energy images
% Returns DEI values

% INITIALIZE THE MATRICES
DEIval = ones(512, 512);
kernel = 1/9 *(ones(3,3));
filter140= zeros(512,512);
filter80 = filter140;

% Same as creating a 3 x 3 averaging filter; Very cost effective
filter140 = filter2(kernel,dicomImage140);
filter80 = filter2(kernel,dicomImage80);

% Only for positive HU values and values for which 80 kVp > 140 kVp
tmp=(filter140>0) & (filter80>100) & (filter80>filter140);
DEIval = ((filter80 - filter140)./(filter80 + filter140)).*tmp;

% PADDING THE ENDS
DEIval(1,:) = 0;
DEIval(512,:) = 0;
DEIval(:,1) = 0;
DEIval(:,512) = 0;

%%%%%%%%%%THE END%%%%%%%%%
APPENDIX B

Saline preparation

Saline was prepared 5 gallons at a time.

122.7 g of di-Sodium Hydrogen Phosphate,

46.7 g of Sodium Phosphate monobasic

140 g of Sodium Chloride

All salts were dissolved in 5 gallons of water to produce saline.