Use of cardiac CT angiography imaging in an epidemiology study - the Methodology of the Multicenter AIDS Cohort Study cardiovascular disease substudy

Kardiyak BT anjiyografik görüntülemenin epidemiyolojik bir çalışmada kullanımı - "The Multicenter AIDS Cohort Study" kardioyovasküler alt çalışmasının metodolojisi

Yalçın Hacıoğlu, Mohit Gupta, Tae-Young Choi, Richard T. George[1], Christopher R. Deible[2], Lisa P. Jacobson[3], Mallory D. Witt, Frank J. Palella[4], Wendy S. Post[1,3], Matthew J. Budoff

Harbor UCLA Medical Center and the Los Angeles Biomedical Research Institute, Torrance, CA-*USA*
[1]Johns Hopkins University, School of Medicine, Baltimore, MD-*USA*
[2]University of Pittsburgh, School of Medicine, Pittsburgh, PA-*USA*
[3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD-*USA*
[4]Northwestern University, School of Medicine, Chicago, IL-*USA*

ABSTRACT

Objective: The methodology for use of cardiac CT angiography (CTA) in low risk populations is not well defined. In order to present a reference for future studies, we present CTA methodology that is being used in an epidemiology study- the Multicenter AIDS Cohort Study (MACS).

Methods: The Multicenter AIDS Cohort Study (MACS) is an on-going multicenter prospective, observational cohort study. The MACS Cardiovascular Disease substudy plans to enroll 800 men (n= 575 HIV seropositive and n=225 HIV seronegative) age 40-70 years for coronary atherosclerosis imaging using cardiac CTA. The protocol includes heart rate (HR) optimization with beta blockers; use of proper field of view; scan length limitation; prospective ECG-gating using the lowest beam voltage possible. All scans are evaluated for presence, extent, and composition of coronary atherosclerosis, left atrial volumes, left ventricular volume and mass and non-coronary cardiac pathology.

Results: The first 498 participants had an average radiation dose of 2.5±1.6 milliSieverts (mSv) for the cardiac CTA study. Overall quality of scans was fair to excellent in 98.6% of studies. There were three significant adverse events-two allergic reactions to contrast and one subcutaneous contrast extravasation.

Conclusion: Cardiac CTA was safe and afforded a low effective radiation exposure to these asymptomatic research participants and provides valuable cardiovascular endpoints for scientific analysis. The cardiac CTA methodology described here may serve as a reference for use in future epidemiology studies aiming to assess coronary atherosclerosis and cardiac anatomy in low risk populations while minimizing radiation exposure. *(Anadolu Kardiyol Derg 2013; 13: 207-14)*

Key words: CT angiography, radiation dose, epidemiological study

ÖZET

Amaç: Kardiyak BT anjiyografinin düşük riskli popülasyonlardaki kullanımı ile ilgili metodolojisi belirsizdir. Gelecekteki bu tür çalışmalara referans oluşturması amacıyla bu makalede "The Multicenter AIDS Cohort Study" kardioyovasküler hastalık (MACS-KAH) alt çalışmasının metodolojisi sunulmaktadır.

Yöntemler: MACS-KAH alt çalışması birçok merkezli, prospektif ve gözlemsel-kohort çalışmadır. Bu çalışmada 40-70 yaş arası 575'i HIV seropozitif ve 225'i HIV seronegatif olmak üzere toplam 800 erkeğin kardiyak BT aracılığıyla koroner görüntülemesi planlanmaktadır. Çalışma protokolü beta blokerlerle kalp hızının optimizasyonu, uygun görüntüleme alanının seçimi, scan uzunluğunun sınırlanması, prospektif EKG tetiklemenin ve olası en düşük ışın voltajının kullanımını içermektedir. Tüm olgular koroner aterosklerozun varlığı, yaygınlığı ve içeriği, sol atriyum hacmi, sol ventrikül hacmi ve kitlesi ve koroner dışı kalp patolojilerin varlığı açısından incelenmektedir.

Bulgular: Çalışmaya alınan ilk 498 deneğin kardiyak BT'sinde ortalama radyasyon dozu 2.5±1.6 milliSievert olarak bulundu. Scanlerin görüntü kalitesi deneklerin %98.6'sında orta ve mükemmel arasında değişmekteydi. İkisi kontrast maddeye alerjik reaksiyon ve biri de kontrast ekstravazasyonu olmak üzere toplam üç olguda beklenmeyen yan etki görüldü.

208 Hacıoğlu et al.
Cardiac CT angiography in epidemiology

Anadolu Kardiyol Derg
2013; 13: 207-14

Sonuç: Bu metodolojinin kullanımı ile kardiyak BT anjiyografinin bilimsel analizlerde değerli kardiovasküler verilerin elde edilmesi amacıyla semptomsuz araştırma deneklerinde düşük etkin radyasyon dozu sağlayarak güvenle kullanımı olasıdır. Dolayısıyla bu metodoloji, gelecekte düşük riskli popülasyonlarda koroner aterosklerozun ve kalp anatomisinin incelenmesini amaçlayan benzer epidemiyolojik çalışmalara referans olarak ışık tutabilir. *(Anadolu Kardiyol Derg 2013; 13: 207-14)*
Anahtar kelimeler: BT anjiyografi, radyasyon dozu, epidemiyolojik çalışma

Introduction

Human immunodeficiency virus (HIV) infection may be associated with increased risk for coronary artery disease, dilated cardiomyopathy, myocarditis, endocarditis, pericardial effusion, and pulmonary arterial hypertension (1-3). Inflammatory changes, endothelial dysfunction and prolonged exposure to antiretroviral protease inhibitor drugs resulting in metabolic changes such as dyslipidemia and lipodystrophy have been suggested as some of the probable predisposing factors. The evidence for accelerated atherosclerosis was chronologically provided by autopsy series, case reports, cross sectional studies using carotid Doppler ultrasound, coronary artery calcium imaging and a few small-scale studies using cardiac computed tomography angiography (CTA) (4-7). At present, there are no published large-scale epidemiology studies that include cardiac CTA to evaluate the prevalence or progression of subclinical coronary atherosclerosis among asymptomatic HIV patients.

Cardiac CTA is a robust non-invasive imaging modality with proven accuracy in diagnosis and quantification of coronary atherosclerosis (8). Besides coronary luminal narrowing, it provides important information about plaque composition (calcified vs. non-calcified) as well as other cardiac or extra-cardiac structures that may be adversely affected by HIV infection (i.e., cardiac chambers, myocardial mass, valves, pericardium, pulmonary vasculature, etc.). However, due to concerns of radiation exposure hazards based on relatively high dose estimates obtained during the early experience with 64-slice CCTA, experts in the field have recommended against its use in the screening of asymptomatic populations, as well as its use in epidemiology studies (8-12).

Nevertheless, the past several years witnessed the development of newer CT technologies and dose reduction protocols (i.e., use of lower field of view, prospective image acquisition protocol, use of lower kV and mA, and dose modulation techniques) that resulted in substantially lower radiation exposures (as low as 1 mSv per study in some reports) than those reported earlier (13-20). Therefore, it is conceivable that the routine implementation of these new techniques could significantly diminish the radiation hazards associated with cardiac CTA imaging, eventually leading to its wider applicability in a broader spectrum of clinical and research settings.

We describe the cardiac CTA methodology used in the Multicenter AIDS Cohort Study (MACS) Cardiovascular Disease (CVD) substudy, so that it may serve as a reference for the use of cardiac CTA in future epidemiology studies.

Methods

Cardiac CTA methodology in the MACS cardiovascular substudy

The MACS-CVD substudy is a prospective multi-center observational epidemiology study that aims to compare the prevalence and progression of subclinical CVD between HIV seropositive and HIV seronegative men. The specific hypothesis of this study is that the metabolic, inflammatory, immunologic, and anthropomorphic changes associated with HIV infection and/or antiretroviral therapy lead to increased risk for subclinical CVD. This is one of the first prospective studies to utilize cardiac CTA in an asymptomatic population, to identify the presence, size, and composition of coronary plaques (including the degree of coronary artery stenosis). The complete study protocol also involves additional limited CT scanning of the abdomen and thigh for adiposity, non-contrast CT for coronary artery calcium (CAC), carotid ultrasound for carotid intimal thickness, carotid plaque, and carotid artery distensibility, as well as phlebotomy for various blood biomarkers. The current manuscript will focus only on the methodology of the coronary atherosclerosis CT imaging acquired with CTA.

The research protocol was approved by the Institutional Review Boards at each clinical site and participants signed informed consent prior to enrolling in the study. This research on human subjects is in accordance with ethical standards of their institution and with the Helsinki Declaration of 1975, as revised in 1983.

Participants

The MACS Cardiovascular Disease (CVD) substudy plans to enroll up to 800 men (n=575 HIV-positive and n=225 HIV-negative) aged 40-70 years, most of whom have already participated in the original coronary artery calcium (CAC) MACS CVD substudy (4).

Eligibility criteria include the ability to give informed consent, age 40-70 years old (inclusively); absence of history of heart surgery (coronary artery bypass graft or valve surgery) or history of coronary angioplasty with or without stent placement and weight <=300 lbs. Participants are excluded from the contrast CT portion of this study, but can participate in the non-contrast portion (which includes coronary artery calcium) if one of the following is present: estimated glomerular filtration rate by the Modification of Diet in Renal Disease equation (GFR/MDRD) obtained within a month of the scan <60 mL/min or urine protein >3 g/L creatinine using a spot urine test; history of contrast allergy; or atrial fibrillation at the time of the scan.

Anadolu Kardiyol Derg
2013; 13: 207-14

Hacıoğlu et al.
Cardiac CT angiography in epidemiology *209*

CT scanners/centers

While the original MACS substudy included noncontrast coronary artery calcium (CAC) scanning with either electron beam tomography (EBT) or multidetector computed tomography (MDCT), the current cardiac CTA study utilizes only 64+ detectors MDCT scanners. CT scanning equipment includes General Electric (GE) LightSpeed VCT (64-slice MDCT, General Electric, USA) at Harbor-UCLA Medical Center and University of Pittsburgh, Siemens Definition 64-slice Dual Source CT (DSCT, Siemens, Germany) at Northwestern University and Toshiba Aquilion One, 320-slice MDCT (Toshiba, Japan) at Johns Hopkins Hospital.

Participant recruitment, screening and preparation

Potentially eligible participants are mailed a brochure describing the MACS cardiovascular substudy. Recruitment and screening occurs in person at a MACS study visit or by phone. Screening is performed for eligibility as described above. All participants undergo serum creatinine testing within a month prior to CT scanning in order to be eligible for IV contrast on the day of their CT scan visit (acceptable estimated GFR is ≥60 mL/min using the *MDRD* equation) (21). Men with contraindications for contrast (e.g. estimated GFR < 60 mL/min or with contrast allergy) receive a non-contrast CT scan only.

On the day of the CT scan, participants are interviewed by a technologist, nurse or physician's assistant at least 30 minutes prior to the procedure. Screening for contraindications for beta-blockers and nitroglycerin is performed. Blood pressure and heart rate are measured and peripheral IV access is obtained. Participants have one intravenous line placed (typically 20 gauge), preferably in an antecubital vein for contrast administration. The participant lies in supine position on the scanner table and is attached to a 12-lead electrocardiographic monitor and an automated blood pressure monitor. Baseline EKG, heart rate, and blood pressure are recorded and reviewed by study personnel. A physician is present at all times during contrast-enhanced MDCT imaging.

Heart rate optimization

Except for the participants undergoing DSCT studies all other participants with initial heart rates of ≥65 beats per minute (BPM) are given beta blocker therapy according to local proto-

cols. Generally, 50 mg of metoprolol is given orally up to one hour prior to the MDCT. If the HR remains >65 BPM, the physician then has an option to either try another oral dose of 50 mg or proceed directly to intravenous metoprolol 2.5 - 5 mg every 5 minutes (maximum 40 mg) until a heart rate of 50-65 BPM is achieved (as long as blood pressure tolerates). Participants may receive IV or oral diltiazem or verapamil if there is a contraindication to using β-blockers (e.g. severe reactive airway disease).

Pre-procedural nitroglycerin

Unless the participant is hypotensive (systolic BP<90 mm Hg supine), nitrate intolerant or received sildanefil (Viagra), tadalafil (Cialis), or vardenafil (Levitra) within 24-48 hours of the study, every participant receives 0.4 mg of sublingual NTG one minute prior to contrast administration in order to improve epicardial vasodilation.

Contrast administration

Based on the preference of each scanning center, either a low osmolar v.s iso-osmolar, non-ionic, iodinated contrast (either iohexol, iopamidol, or iodixanol) is usually administered at a rate of 5 mL/sec as an IV infusion of, on average, 50-60 mL (max.70 mL), based on the participant's size after completion of the non-contrast CT studies. Based on the preference of each scanning center either a test bolus or an automated bolus tracking feature is used to assess contrast bolus arrival and optimize image quality. Participants are asked to hold their breath during scanning for up to 10 seconds.

CT image acquisition and radiation dose reduction methods

The main radiation dose reduction methods used in the MACS Cardiovascular Substudy are listed in Table 1. First, scout images are obtained in order to determine the scan range in the anterior-posterior and lateral views. In addition, all CTAs are preceded by a non-contrast cardiac CT scan, which is also used to determine the range of the CTA. Whenever possible the field of view (FOV) on the axial plane is limited to 25 cm in addition to using a proper size cardiac bowtie filter (small for GE scanners and medium for Toshiba Aquilion One scanner) so that the X-ray beam can be limited mostly to cardiac structures (20-22). Utmost effort is exerted to limit the scan length (the z-axis of the chest area imaged) as well.

Table 1. Radiation dose reduction methods used in the MACS Cardiovascular substudy

Dose Reduction Technique	Description
Limitation of the field of view	Limit xy field of view (FOV) using proper size cardiac bowtie filter during image acquisition (FOV 25 cm with small bowtie filter for GE and medium bowtie filter for Toshiba). The FOV is centered on the heart with very minimal display of non-cardiac structures
Limitation of the scan length	Limit scan length (z-axis of chest coverage). This requires efficient use of scout or CAC images for determination of the shortest optimal scan length (usual range 128-160 mm) so that all cardiac structures are optimally visualized along the z-axis starting from 1cm above the left main artery origin to 1 cm below the diaphragm
Prospective ECG triggered image acquisition	Obtaining images only during one phase (± padding) of cardiac cycle (mid-diastole), rather than continuous imaging during the entire cardiac cycle for the majority of studies
Low tube voltage settings	Using the lowest tube voltage possible (preferably 80-100 kV, max. 120kV) based on body habitus

CAC - coronary artery calcium, ECG - electrocardiogram, FOV - field of view, kV - kilovolt

210 Hacıoğlu et al.
Cardiac CT angiography in epidemiology

Anadolu Kardiyol Derg
2013; 13: 207-14

This requires efficient use of the scout and/or CAC images for determining the shortest scan length (usual range 128-160 mm) that includes all cardiac structures along the z-axis, starting from 1cm above the left main artery origin to 1 cm below the diaphragm.

The goal is for all studies to use prospective ECG triggering. This technique requires obtaining images only during one phase range of the cardiac cycle with or without some limited padding (75% phase±5% padding), rather than continuous helical imaging (retrospective ECG-gating) during the entire cardiac cycle. This technique is preferred over retrospective ECG-gating imaging unless the heart rate is elevated or there is significant heart rate variability. For the Toshiba scanner, the goal is to perform a "one beat" prospective ECG-triggered scan. If the heart rate is elevated, then a "two beat" prospective ECG- triggered scan is performed.

The fourth method is the use of a reduced tube voltage (use of 80 or 100 kVp for participants with a body mass index <25 kg/m^2, rather than the typically employed 120 kVP), which has been shown to reduce radiation exposure by up to 44.8% independent of other techniques (23, 24).

Each measure undertaken contributes to reducing radiation doses to a range acceptable for use in asymptomatic cohorts. The radiation dose per participant was estimated to fall in the range of 2-5 mSv depending on body mass index (BMI), cardiac height and heart rate. The specific scanning settings at each CT center are shown in Table 2.

Data transmission

When studies are completed they are transmitted to the core CT reading center (Los Angeles Biomedical Research Institute at Harbor/UCLA Medical Center) and are read using a dedicated workstation (GE Advantage Workstation® (AW)-version 4.4, GE Healthcare, Milwaukee, WI) by one experienced reader (>10 years of expertise) who is blinded to participant demographic information.

Table 2. CTA scanning parameters by CT site

	Center 1	Center 2	Center 3	Center 4
Scanner type, # of detectors	GE LightSpeed, 64	GE LightSpeed, 64	Siemens Somatom Definition, 64	Toshiba Aquilion One, 320
Image acquisition protocol	Prospective for all if HR<65/min; otherwise retrospective	Prospective for all if HR<65/min; otherwise retrospective	Prospective for all§	Prospective for all; two beats scanning‡ if HR≥ 65/min
Tube voltage, kV	For BMI<25: 80-100 For BMI≥25: 100	100	For BMI <25: 80-100 For BMI ≥25: 100	For BMI<25: 100 For BMI≥25: 120
Tube current, mA	mA (BMI) 350 (<25) 550 (25-30) 750/650* (>30)	mA (BMI) 350 (<25) 550 (25-30) 750 (>30)	200	mA (BMI) 550 (<25) 500/490¶ (25-30) 580/490¶ (>30)
Collimation, mm	64x0.625	64x0.625	64x0.6	320x0.5
Rotation time, s	0.35	0.35	0.33	0.35
Reconstruction kernel	Standard	Standard	B26	FC43 (standard)
Acquisition window (phase)£	70-80%	70-80%	70-80%	70-80%
Reconstructed slice thickness, mm	0.625	0.625	0.75	0.5
Reconstruction interval, mm	0.625	0.625	0.40	0.25
Contrast medium	Omnipaque®	Visipaque®	Isovue-370®	Isovue-370®
Contrast rate, mL/s	4-5	5	Determined by Medrad P3T software	5-6
Contrast amount, mL	Based on weight: 50 for <60 kg 60 for 60-99 kg 70 for >100 kg	Based on weight: 50 for <60 kg 60 for 60-99 kg 70 for >100 kg	Determined by Medrad P3T software based on weight	Based on weight: 50 for <60 kg 60 for 60-99 kg 70 for >100 kg

§Exceptions require approval by the radiologist
‡Prospective ECG gated scanning with total exposure time of 700 ms over portions of two R-R intervals
†This is the current protocol since January 2011; prior to that it was BMI based, in the range of 80-120 kV
*For retrospective ECG gated imaging protocol
¶For two beats scanning with Toshiba Aquilion One scanner
£For prospective ECG gated imaging

BMI - body mass index, CT - computerized tomography, CTA - computerized tomography angiography, ECG - electrocardiogram, HR - heart rate

Anadolu Kardiyol Derg
2013; 13: 207-14

Hacıoğlu et al.
Cardiac CT angiography in epidemiology   *211*

Curved maximum intensity projection (MIP) and multiplanar reconstructions are performed for each coronary artery segment at the end-diastolic frame or the frame with the least motion artifact. Based on the curved MIP, the reader identifies an area of abnormality and determines the point of minimum luminal diameter within the abnormal area. Multiplanar reformatting is also used to generate cross-sectional images of coronary segments using semi-automated software (AW 4.4, GE Healthcare, Milwaukee, WI). This yields a vessel centerline using the full-width-half-maximum standard method to delineate the contrast-filled vessel, as well as automatic maximum and minimum diameters at any cross-section along the vessel centerline. A cross-sectional 5 mm MIP image is reconstructed at this location and semi-automatic software is used to outline the intimal surface providing cross-sectional vessel area. In cases where coronary segments are normal, the most proximal cross-sectional image is used for analysis. CT values are measured using the most visible images at each site of the coronary arteries, such as axial source or multiplanar images of the long-axis. All data sets are evaluated based on the modified 15-segment model of the American Heart Association (25). The right coronary artery is defined to include segments 1-4, the left main artery and the left anterior descending (LAD) artery to include segments 5-10, and the left circumflex artery (LCX) to include segments 11-15. The intermediate artery (ramus artery), if present, is designated as segment 16. Side branches are used as anatomical landmarks to define coronary segments.

Assessment of the presence and extent of coronary artery plaque and stenosis

The CT reader interactively uses axial images, multi-planar reconstructions and maximum intensity projections to assess the presence and size of plaque and the degree of luminal narrowing and stenosis in all assessable coronary segments. Each segment is graded as to whether it has sufficient diameter and image quality to be accessed. The size of plaque and the percentage of coronary arterial stenosis are estimated from cross-sectional images obtained from a curved multiplanar CTA reconstruction of standardized coronary segments. Plaque size is graded as 0=no plaque, 1=mild, 2=moderate, or 3=severe. Segment stenosis is defined as 0=no plaque, 1=1-29% (minimal) stenosis, 2=30-49% (mild) stenosis, 3=50-69% (moderate) stenosis, or 4=>70% (severe) stenosis. Diameter stenosis is reported by selecting the most narrowed diameter even if the plaque is eccentric. The extent of atherosclerosis is expressed as the total plaque score (TPS) and is determined by summing the plaque size scores for all assessable coronary segments with any plaque (either calcific, noncalcific, or mixed) up to a maximum score of 45. The stenosis scores of all 15 individual segments are summed to yield a total stenosis score (TSS) ranging from 0 to 60.

Composition of coronary atherosclerotic plaque

Plaque is evaluated from both axial source images and multiplanar reconstruction images of the long axis at each site of the coronary arteries. Calcified atherosclerotic plaque is defined as any structure with a density greater than the contrast-enhanced lumen that can be visualized separately from the lumen, can be assigned to the coronary artery wall, and can be identified in at least two independent planes. Non-calcified atherosclerotic plaque is defined as any discernible structure that can be clearly assignable to the vessel wall (which has a CT density less than the contrast-enhanced coronary lumen but greater than the surrounding connective tissue) and can be identified in at least two independent planes (26). Each coronary segment is classified as either normal or containing non-calcified plaque, mixed plaque (<50% of plaque area occupied by calcium) or calcified plaque. Standard display settings are used for the evaluation of the contrast-enhanced CT scans (window width 800 Hounsfield units; window center 250 HU). Reviewers independently evaluate the contrast-enhanced scans by assessment of the axial slices of multiplanar reformations and of three thin-slab maximum intensity projections. Oriented along the heart axis, the thin-slab (5 mm thickness, 1-mm increment) maximum intensity projections are reconstructed perpendicular to one another.

Left ventricular volume and mass

Measurements are made for left ventricular (LV) volume, mass and left atrial (LA) volumes using Simpson's method of discs, which has been previously validated (27). Estimation of end-diastolic LV volume is possible with the help of a prediction model using LV and LA volumes at the 75% phase [LV EDV=(1.021×75% phase LV volume) + (0.259×75% phase LA volume), adjusted R (2)=0.995] (28).

Non-coronary cardiac findings

Cardiac CTAs are also evaluated for major non-coronary cardiac findings that may alter patient management: aortic disease, valvular disease, pericardial disease, interatrial and interventricular shunts, and aneurysms. According to individual institutional practice, scans are read for non-cardiac incidental findings by a radiologist and/or for findings of clinical importance that are referred to a radiologist for interpretation, and then reported to the PI. The clinical follow-up of lung nodules is advised based on the Fleischner Society Recommendations (29).

Assessments for quality assurance and contrast medium, and radiation dose safety

Quality assurance of CT images is performed using five distinct measures. First, each CT scan is visually inspected by the data manager at the core CT lab for compliance with the protocol, including appropriate kilovolts (kVs), milliAmperes (mAs), reconstruction field of view, slice thickness and phase reconstructions, as well as radiation dose length product. Then the expert CT reader analyzes each image for adequate breath hold, presence of motion artifacts, and inclusion of all parts of the heart and descending thoracic aorta. Third, a contrast-to-noise ratio of the distal left anterior descending artery is calculated for each scan as a quantitative metric of image quality. Fourth, a randomly selected 5% of cases are measured for image quality assurance by the primary investigator as well as the CT reader. Fifth, CT scanners at each site perform daily calibration.

212 Haciǒglu et al.
Cardiac CT angiography in epidemiology

Anadolu Kardiyol Derg
2013; 13: 207-14

Image quality is assessed by looking at the axial data (representative of the X- and Y-axes resolution) and the coronal reformat slice (representative of the Z-axis resolution). All CTA scans are evaluated for presence or absence of slab, blurring, and partial volume-averaging artifacts. Image quality is graded for individual coronary artery segments and for the entire study.

One reader, blinded to clinical and scan parameters, scores each study. Parameters assessed include participant motion, respiratory motion, cardiac motion, image noise (signal to noise ratios), contrast opacification and segment-based interpretability. Overall image quality is scored using a four-point Likert scale (30). Segments that cannot be evaluated are given a score of 4, which corresponds to a lack of vessel wall definition due to marked motion artifacts, poor vessel opacification, prominent structural discontinuity, or high image noise–related blurring. A score of 3 corresponded to some motion artifacts or noise-related blurring, fair vessel opacification, or minimal structural discontinuity; a score of 2 indicates minor motion artifacts or noise-related blurring, good vessel opacification, and no structural discontinuity; and a score of 1 implies absence of motion artifacts or noise-related blurring, excellent vessel opacification, and no structural discontinuity.

Each participating center is required to monitor vigilantly patient radiation and contrast doses via field site data collected and intervene to improve safety on a timely and ongoing basis. The contrast and radiation dosage of each scan is reviewed. If CTA mean radiation doses exceed 7 mSv or contrast doses exceed 100 cc, the CTA control liaison (CTA-CL) will initiate remedial actions at the enrolling site. Feedbacks that may be provided to the scanner technologist include suggestions for X-ray beam voltage reduction, adherence to prospective gating, limiting the field of view or scan length and improvement of heart rate optimization methods. The CTA-CL is also required to notify the site primary investigator regarding any of these issues.

Results

Radiation safety and quality assurance survey results

The initial survey for quality assurance and radiation safety including estimated effective dose (ED), dose length product (DLP), X-ray beam voltage (kV), image quality, image noise and aorta attenuation was based on findings from the first 498 participants (mean age 54±6 years, all men) of the MACS CVS substudy (Table 3). Optimal heart rate (HR<65 BPM) was achieved in 74.5% (371/498) of participants. Prospective gating was performed in 96.8% of participants (482/498). The effective radiation dose (ED) was calculated using the following formula: (ED=DLP x Conversion factor (0.014 for chest; 0.015 for abdomen; 0.0008 for legs), was 2.5±1.6 mSv (mean±SD) for cardiac CTA studies; and total of 4.6±1.9 mSv for all CT studies combined, including CAC, cardiac CTA, abdominal and thigh scans.

Radiation doses delivered were low for all scanners used in the study, with mean doses of 1.8±1.6 mSv for scans obtained using the General Electric VCT (64 detector system), 2.6±1.6 mSv for the Siemens DSCT, and 3.3±1.2 mSv for studies obtained with the Toshiba Aquilion One (320 detector system) (Table 3). The

image noise was low and proportional to the effective radiation doses. There have been 7 cardiac CTA procedures with doses over 7 mSv. Six of these studies involved retrospective protocols undertaken because of variable heart rates or heart rates above threshold, and some after a prospective scan was felt to be inadequate. Only 3 scans involved radiation exposures >10 mSv (including the non-contrast portion) with the highest exposure being 17.6 mSv. The seventh was a scan using a "two beat" prospective ECG-gated protocol (dose for the cardiac CTA was 7.8 mSv). Further training and clarification of the research protocol (only one CTA per participant) subsequently minimized these protocol deviations, with one site deciding not to perform any further retrospective scans (Northwestern).

Generally the CT scans were well tolerated. There were only two reported allergic reactions to contrast-one involving urticaria, and other nasal congestion and itchy throat. Both reactions resolved with conservative medical therapy. One participant experienced contrast extravasation due to an infiltrated IV line and this resolved with conservative therapy.

To date, there have been no cases of contrast induced nephropathy or radiation induced cancers detected. We did not measure DNA fracture rates as part of this study.

Discussion

We herein describe a cardiac CTA methodology that implements multiple radiation- reducing measures as well as undertakes numerous careful cardiovascular structural measurements that, in sum, provide valuable cardiovascular endpoint data for scientific analysis while minimizing the radiation exposure per study (<7 mSv). The mean effective radiation dose for the cardiac portion of the CTA was only 2.5±1.6 mSv. In addition, there were very few participants who received CTA radiation doses over 7 mSv (7/498 or 1.4%). Similarly, the incidence of significant adverse events (a mild allergic reaction and IV contrast extravasation) was low (3/498=0.6%) and had been described in the study consent form.

The efficacy and safety of the measures undertaken in our study to reduce radiation dose have been previously evaluated in numerous other reports. For example, the use of a proper bowtie filter was suggested as an important measure for limiting radiation dose in a letter communication by Budoff et al. (20) in which it was proposed that reducing the FOV by using a small instead of a medium cardiac bowtie filter may result in up to a 40% radiation dose reduction (from 13.4 mSv to 8 mSv with retrospective imaging, and to a level as low as 1 mSv with prospective imaging) (19). Use of bowtie filters also result in lower radiation exposure.

In another study by Gopal et al. (14) the CAC scan was used in order to limit the cranio-caudal coverage scan length (ideally covering only the area from ~1 cm above the visualized top of the coronary arteries extending down to 1 cm below the distal border of posterior descending artery). Using this method the scan length was reduced by ~ 3-4 cm per study, which translated into a ~ 30% overall radiation dose reduction, despite the added 1. 2 mSv radiation due to CAC scanning.

Anadolu Kardiyol Derg
2013; 13: 207-14

Hacıoğlu et al.
Cardiac CT angiography in epidemiology   *213*

Table 3. Quality and radiation safety data of first 498 CTA studies by CT scanner type

Variables		All participants (n=498)	GE LightSpeed (n=205)	Siemens DSCT (n=149)	Toshiba 320 (n=144)
Age , years		55.5±6.5	54.7±6.5	55.2±5.9	57.1±6.8
Heart rate, bpm		60±8	60±7	63±8	57±7
DLP - Cardiac CTA only, mGycm		178.5±114	131±112.5	188.7±114.1	235.5±83.9
Effective dose - Cardiac CTA only, mSv		2.5±1.6	1.8±1.6	2.6±1.6	3.3±1.2
DLP - Entire study*, mGycm		330.3±135.6	276.6±131.4	348.6±149.6	387.9±91.2
Effective dose - Entire study*, mSv		4.6±1.9	3.9±1.9	4.9±2.1	5.4±1.3
Tube voltage, kV, frequency (%)	80	22/498 (4.4)	21/205 (10.2)	1/149 (0.7)	0/144 (0)
	100	337/498 (67.7)	181/205 (88.3)	93/149 (62.4)	63/144 (43.8)
	120	139/498 (27.9)	3/205 (1.5)	55/149 (36.9)	81/144 (56.2)
Overall image quality, frequency (%)	Excellent	268/498 (53.8)	95/205 (46.3)	89/149 (59.7)	84/144 (58.3)
	Good	185/498 (37.2)	85/205 (41.5)	53/149 (35.6)	47/144 (32.6)
	Fair	38/498 (7.6)	21/205 (10.2)	5/149 (3.4)	12/144 (8.4)
	Poor	7/498 (1.4)	4/205 (2)	2/149 (1.3)	1/144 (0.7)
Image noise		33.4±9.8	36.9±9.5	31.6±8.9	30.7±9.8
Aortic attenuation, HU		444.1±82.4	429.8±88.5	456.5±85.9	450.6±66.7

Data are presented as mean±SD and percentage values
* Also includes non-contrast CT scans, including coronary artery calcium, and single slices through the abdomen and thigh.
bpm - beats per minute, CT - computerized tomography, CTA - computerized tomography angiography, DLP - dose length product, DSCT - dual source CT, HU - Hounsfield unit,
SD - standard deviation

Moreover, Shuman et al. (16) showed that, without using any other dose reduction technique, prospective ECG-triggering could reduce the mean radiation dose by 77% compared to retrospective ECG-gating (4.2 mSv vs. 18.1 mSv, p<0.01), without compromising image quality or diagnostic accuracy (15). Another study similarly reported that the use of prospective ECG-triggering reduced radiation exposure by 79% without compromising image quality when compared to traditional retrospective ECG-gated acquisition (16).

The fourth method employed in our study, which is the use of a reduced tube voltage (use of 80-100 kV for participants <85 kg rather than typically employed 120 kV) was previously studied by Hausleiter et al. (18) in patients undergoing retrospective ECG-gating CTA with either 16-slice or 64-slice CT scanners. In this study researchers demonstrated that, compared to 120 kV voltage, the use of 100 kV could lower the radiation exposure by 22% when using 16 slice-scanners and 43% with 64-slice scanners, independent of any other techniques.

Further technologic advances in radiation dose reduction with cardiac CTA have been implemented since the inception of this trial. Iterative reconstruction is now available on all scanners, resulting in the achievement of additional radiation dose reductions of 30-40% (31). Furthermore, new detectors are now being introduced that allow for further radiation dose reductions, that will further enhance the safety of this tool in large cohort studies and patient populations.

Conclusion

If proven feasible and efficient, the methodologies that we describe in this report may enable the use of cardiac CTA as a safe and effective screening tool of choice for detection of subclinical coronary atherosclerosis and structural cardiac pathologies, even in low risk populations such as in those that participate in epidemiologic population-based studies.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

214 Hacıoğlu et al.
Cardiac CT angiography in epidemiology

Anadolu Kardiyol Derg
2013; 13: 207-14

References

1. Khunnawat C, Mukerji S, Havlichek D Jr, Touma R, Abela GS. Cardiovascular manifestations in human immunodeficiency virus-infected patients. Am J Cardiol 2008; 102: 635-42. **[CrossRef]**
2. Baker JV, Lundgren JD. Cardiovascular implications from untreated human immunodeficiency virus infection. Eur Heart J 2011; 32: 945-51. **[CrossRef]**
3. DAD Study Group, Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte Ad, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007; 356: 1723-35. **[CrossRef]**
4. Kaplan RC, Kingsley LA, Gange SJ, Benning L, Jacobson LP, Lazar J, et al. Low CD4+ T-cell count as a major atherosclerosis risk factor in HIV-infected women and men. AIDS 2008; 22: 1615-24. **[CrossRef]**
5. Kingsley LA, Cuervo-Rojas J, Muñoz A, Palella FJ, Post W, Witt MD, et al. Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study. AIDS 2008; 22: 1589-99. **[CrossRef]**
6. Lo J, Abbara S, Shturman L, Soni A, Wei J, Rocha-Filho JA, et al. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. AIDS 2010; 24: 243-53. **[CrossRef]**
7. d'Ettorre G, Francone M, Mancone M, Ceccarelli G, Ascarelli A, Vullo F, et al. Significant coronary stenosis detected by coronary computed angiography in asymptomatic HIV infected subjects. J Infect 2012; 64: 82-8. **[CrossRef]**
8. Mowatt G, Cook JA, Hillis GS, Walker S, Fraser C, Jia X, et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. Heart 2008; 94: 1386-93. **[CrossRef]**
9. Hausleiter J, Meyer T, Hermann F, Hadamitzky M, Krebs M, Gerber TC, et al. Estimated radiation dose associated with cardiac CT angiography. JAMA 2009; 301: 500-7. **[CrossRef]**
10. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation 2006; 114: 1761-91. **[CrossRef]**
11. Bluemke DA, Achenbach S, Budoff M, Gerber TC, Gersh B, Hillis LD, et al. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention, and the Councils on Clinical Cardiology and Cardiovascular Disease in the Young. Circulation 2008; 118; 586-606. **[CrossRef]**
12. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA 2007; 298: 317-23. **[CrossRef]**
13. Raff GL, Chinnaiyan KM, Share DA, Goraya TY, Kazerooni EA, Moscucci M, et al. Radiation dose from cardiac computed tomography before and after implementation of radiation dose-reduction techniques. JAMA 2009; 301: 2340-8. **[CrossRef]**
14. Gopal A, Mao SS, Karlsberg D, Young E, Waggoner J, Ahmadi N, et al. Radiation reduction with prospective ECG-triggering acquisition using 64-multidetector computed tomographic angiography. Int J Cardiovasc Imaging 2009; 25: 405-16. **[CrossRef]**
15. Gopal A, Budoff MJ. A new method to reduce radiation exposure during multi-row detector cardiac computed tomographic angiography. Int J Cardiol 2009; 132: 435-6. **[CrossRef]**
16. Shuman WP, Branch KR, May JM, Mitsumori LM, Lockhart DW, Dubinsky TJ, et al. Prospective versus retrospective ECG gating for 64-detector CT of the coronary arteries: comparison of image quality and patient radiation dose. Radiology 2008; 248: 431-7. **[CrossRef]**
17. Hirai N, Horiguchi J, Fujioka C, Kiguchi M, Yamamoto H, Matsuura N, et al. Prospective versus retrospective ECG-gated 64-detector coronary CT angiography: assessment of image quality, stenosis, and radiation dose. Radiology 2008; 248: 424-30. **[CrossRef]**
18. Hausleiter J, Meyer T, Hadamitzky M, Huber E, Zankl M, Martinoff S, et al. Radiation dose estimates from cardiac multislice computed tomography in daily practice: impact of different scanning protocols on effective dose estimates. Circulation 2006; 113: 1305-10. **[CrossRef]**
19. Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, et al. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J 2010; 31: 340-6. **[CrossRef]**
20. Budoff MJ. Ethical issues related to lung nodules on cardiac CT. AJR Am J Roentgenol 2009; 192: 146. **[CrossRef]**
21. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461-70.
22. Geleijns J, Salvadó Artells M, de Bruin PW, Matter R, Muramatsu Y, McNitt-Gray MF. Computed tomography dose assessment for a 160 mm wide, 320 detector row, cone beam CT scanner. Phys Med Biol 2009; 54: 3141-59. **[CrossRef]**
23. Budoff MJ, Waggoner J, Ahmadi N, Pal RS, Sarlak B, Honoris L, et al. Substantial radiation dose reduction in 64-multidetector cardiac computed tomographic angiography by using lower X-ray energy during scanning. J Am Coll Cardiol 2008; 51: 148.
24. Blankstein R, Bolen MA, Pale R, Murphy MK, Shah AB, Bezerra HG, et al. Use of 100 kV versus 120 kV in cardiac dual source computed tomography: effect on radiation dose and image quality. Int J Cardiovasc Imaging 2011; 27: 579-86. **[CrossRef]**
25. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975; 51: 5-40. **[CrossRef]**
26. Iwasaki K, Matsumoto T, Aono H, Furukawa H, Samukawa M. Prevalence of subclinical atherosclerosis in asymptomatic diabetic patients by 64-slice computed tomography. Coron Artery Dis 2008; 19: 195-201. **[CrossRef]**
27. Lin FY, Devereux RB, Roman MJ, Meng J, Jow VM, Jacobs A, et al. Cardiac chamber volumes, function, and mass as determined by 64-multidetector row computed tomography: mean values among healthy adults free of hypertension and obesity. JACC Cardiovasc Imaging 2008; 1: 782-6. **[CrossRef]**
28. Khatri PJ, Tandon V, Chen L, Yam Y, Chow BJ. Can left ventricular end-diastolic volumes be estimated with prospective ECG-gated CT coronary angiography? Eur J Radiol 2012; 81: 226-9. **[CrossRef]**
29. MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology 2005; 237: 395-400. **[CrossRef]**
30. Brodoefel H, Tsiflikas I, Burgstahler C, Reimann A, Thomas C, Schroeder S, et al. Cardiac dual-source computed tomography: effect of body mass index on image quality and diagnostic accuracy. Invest Radiol 2008; 43: 712-8. **[CrossRef]**
31. Halliburton SS, Abbara S, Chen MY, Gentry R, Mahesh M, Raff GL, et al. SCCT guidelines on radiation dose and dose-optimization strategies in cardiovascular CT. J Cardiovasc Comput Tomogr 2011; 5: 198-224. **[CrossRef]**