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Quantitative coronary arterial stenosis assessment by multidetector CT and invasive coronary angiography for identifying patients with myocardial perfusion abnormalities by SPECT

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EPÍGRAFE

A DEUS,

Aos meus pais, que sempre me apoiaram incondicionalmente e acreditaram nos meus sonhos.

Aos meus filhos, irmã , família e amigos.

À minha Esposa, minha companheira.

RESUMO

Este trabalho consiste na comparação de diferentes métodos de imagem utilizados na prática clínica para a detecção da doença coronariana isquêmica, umas das maiores causas de mortalidade nos países desenvolvidos, utilizando como base o estudo multicêntrico Internacional, Core 64. Através de uma análise retrospectiva foram selecionados 63 pacientes de um total de 405 do estudo principal Core 64 que tinham realizado, além da Tomografia Computadorizada e da Cinecoronariografia, a Cintilografia de Perfusão Miocárdica com o objetivo principal de avaliar a correlação anátomo-fisiológica entre os diferentes métodos de imagem na avaliação da doença coronariana de causa obstrutiva. Para isto, foram identificadas através da avaliação anatômica quantitativa, tanto pela tomografia quanto pela cinecoronariografia, estenoses coronarianas causando obstruções entre 30 e 80% do lúmen arterial e correlacionadas com a presença de defeitos perfusionais quantificados pela cintilografia de perfusão miocárdica equivalentes ao mesmo território coronariano. Após a análise estatística, constatou-se que tanto a tomografia como a cinecoronariografia apresentam sensibilidade e especificidade apenas moderadas para prognosticar as alterações perfusionais detectadas pela cintilografia de perfusão miocárdica; no entanto, ambos os métodos são complementares e de fundamental importância na prática clínica para o manejo diagnóstico e terapêutico dos pacientes portadores da doença coronariana isquêmica.

Palavras-chave: Tomografia Computadorizada de múltiplos detectores, Cinecoronariografia, Cintilografia de Perfusão Miocárdica, Doença Arterial Coronariana.

ABSTRACT

This work is related to a comparison between different modalities of imaging for the detection of obstructive coronary artery disease causing myocardial ischemia, one of the main cause of death in developed countries, using as base the multicenter trial Core 64. A retrospective analysis was performed using a subgroup of 63 patients of a total of 405 to evaluate the diagnostic accuracy of Multi-Detector Computed Tomography Angiography (MDCTA) and Conventional Coronary Angiography in detecting myocardial ischemia identified by Myocardial Perfusion Imaging (SPECT). Threshold of 30-80% of coronary artery stenosis identified by MDCTA and conventional coronary angiography were setted and correlated to the presence of myocardial ischemia of the same coronary artery territory. After statistical analyses, a similar modest accuracy for quantitative coronary arterial stenosis assessment by both QCTA and QCA for identifying patients with myocardial perfusion were found; however either MDCTA, conventional coronary angiography and SPECT are complementary methods and play an import roll not only diagnosing but guiding clinical treatment in patients with coronary artery disease.

Keywords: Multi-Detector Computed Tomography Angiography, Conventional Coronary Angiography, Myocardial Perfusion Imaging, Coronary Artery Disease

Sumário

LISTA DE ABREVIATURAS/SIGLAS

DAC – Doença Arterial Coronariana

OMS – Organização Mundial de Saúde

IBGE – Instituto Brasileiro de Geografia e Estatística

IVUS – Ultrassom intracoronário

CFR – Fluxo de Reserva Coronariano

QCA – Angiografia Convencional Quantitativa

FFR – Fluxo de Reserva Fraccional

CPM– Cintilografia de Perfusão Miocárdica

ECG – Eletrocardiograma

TCMD –Tomografia Computadorizada de Múltiplos Detectores

1. INTRODUÇÃO

1.1 Doença Arterial Coronariana (DAC)

A doença arterial coronariana (DAC) caracteriza-se pela insuficiência de irrigação sanguínea no coração, mais especificamente no miocárdio, que é feita pelas artérias coronárias. Está diretamente relacionada ao grau de obstrução do fluxo sanguíneo pelas placas ateroscleróticas, resultando em estreitamento das artérias coronárias (estenose), o qual, devido à redução do fluxo sanguíneo coronariano, diminui a chegada do oxigênio ao miocárdio causando o processo de isquemia (1).

Dados da Organização Mundial da Saúde (OMS) revelam que a DAC é a maior causa global de morbi/mortalidade causando aproximadamente cerca de 7.000.000 óbitos/ano (2). No Brasil, segundo a Síntese de Indicadores Sociais de 2002, realizada pelo Instituto Brasileiro de Geografia e Estatística (IBGE), as doenças cardiovasculares se destacam como a principal causa de mortes no País (28,8% para homens e 36,9% para mulheres), em todas as regiões e estados (3).

A realização de seu diagnóstico precoce é de extrema importância uma vez que propicia, em casos menos graves, adequadas medidas terapêuticas não invasivas e preventivas e, nos casos mais graves, uma intervenção curativa antes do desenvolvimento de complicações como o infarto agudo do miocárdio.

Somente nos Estados Unidos, são atendidos nas salas de emergência dos hospitais, aproximadamente 6.000.000 de pacientes por ano com suspeita de doença arterial coronariana isquêmica, apresentada como infarto agudo do miocárdio (4). Cerca de 1.000.000 desses pacientes são diagnosticados como portadores de infarto agudo do miocárdio e perto de 11.000 pacientes por ano são inadequadamente dispensados do pronto-socorro, levando a índices de mortalidade próximos a 25% (5).

A partir destes dados, verifica-se a importância de se adotarem medidas preventivas objetivando a redução de tão desfavorável realidade. Os mesmos demonstram a importância e a necessidade da realização de testes não invasivos nesses indivíduos, que permitam detectar a presença de doença arterial coronária obstrutiva e, assim, encaminhá-los ao devido tratamento.

1.2 Cinecoronariografia

A introdução da cinecoronariografia na década de 60, ampliou os conhecimentos sobre anatomia, fisiologia, físiopatogenia, diagnóstico e tratamento da doença coronariana, sendo reconhecida como método padrão ouro na avaliação anatômica da doença coronariana de causa obstrutiva (6), sendo dessa forma indispensável no manejo terapêutico do paciente coronariano.

No entanto, nas últimas décadas, a importância do diagnóstico da relevância isquêmica das lesões coronarianas tem se mostrado como um contraponto importante sobre a abordagem anatômica.

Estudos recentes (7) revelam que a cinecoronariografia tem um benefício terapêutico maior quando realizada em pacientes portadores de doença aterosclerótica hemodinamicamente significativa sendo, portanto, de fundamental importância a sua utilização nessa doença. Ainda não está claro se a análise anatômica das lesões ateroscleróticas é capaz de prognosticar a relevância hemodinâmica dessas lesões, mas sabemos, por exemplo, que a avaliação anatômica intraluminal através do ultrassom intracoronário (IVUS) tem uma boa correlação com a avaliação hemodinâmica através da análise do fluxo de reserva coronariano (CFR) (8). Por outro lado, a angiografia convencional quantitativa (QCA) tem uma fraca correlação com a análise de fluxo de reserva fracional (FFR) provavelmente por suas limitações na análise da complexa geometria luminal coronariana (9-12).

Portanto, novos estudos tornam-se indispensáveis para um melhor entendimento dessa correlação anatomofisiológica trazendo dessa forma um maior benefício clínico na conduta terapêutica dos pacientes coronarianos.

1.3 Cintilografia de Perfusão Miocárdica

Desde sua introdução na prática clínica, em 1964, e até mais recentemente (13), a Cintilografia de Perfusão Miocárdica (CPM) é considerada indicação prioritária para pacientes com suspeita de DAC, sendo preferencialmente associada ao estresse, físico ou farmacológico. Segundo a I Diretriz da Sociedade Brasileira de Cardiologia sobre Cardiologia Nuclear (14), a CPM é especialmente indicada em pacientes nos quais haja dificuldades para a interpretação adequada do eletrocardiograma (ECG) de esforço. Em busca de aprimorar a definição desse método não invasivo, foram introduzidos, na prática clínica, programas de computador que permitiram a realização da CPM em cortes tomográficos (15), incrementando a capacidade de identificar doença coronária em números superiores a 90% dos casos. Isto transformou a CPM no método não invasivo mais sensível (16), apresentando especificidade de 93% (17) sendo, desta forma, reconhecido como método padrão ouro para a avaliação da isquemia miocárdica causada pela DAC. Possibilita o diagnóstico e manejo de pacientes sintomáticos e pacientes de risco intermediário, com teste de esforço duvidoso, na suspeita de infarto do miocárdio (18), reduzindo assim os índices de morbi/mortalidade dessa doença. No entanto, estudos recentes (17) demonstram que a sua correlação anátomo-funcional com a lesão estenótica nem sempre é possível, resultando em muitos casos, em divergências no manejo clínico desses pacientes.

1.4 Tomografia Computadorizada de Múltiplos Detectores

A tomografia computadorizada de múltiplos detectores (TCMD) é um excelente método no diagnóstico anatômico das doenças coronarianas obstrutivas, mostrando alta acurácia na detecção de placas ateroscleróticas calcificadas e lipídicas e na identificação da obstrução do lúmen arterial causada por estas lesões (19-20). Porém, não está claro na literatura o quanto esse método é capaz de prever o grau de isquemia miocárdica detectável pela cintilografia miocárdica.

Recentes estudos (21-22) utilizando a tomografia computadorizada de 64 detectores, indicaram que a tomografia é um método mais acurado que a angiografia convencional para excluir significantes defeitos perfusionais diagnosticados por CPM.

Além disso, a angiotomografia coronariana compartilha algumas das habilidades da análise intraluminal do ultrassom intravascular, por exemplo, permitindo a análise luminal segmentar em cortes bi e tridimensionais, aferindo de forma acurada as dimensões luminais em diferentes planos de orientação (Axial, sagital, coronal etc.) De fato, quando comparados com o ultrassom intravascular, as medidas do lúmen realizadas pela tomografia têm uma melhor concordância do que as medidas realizadas através da cinecoronariografia (23).

Um estudo recente (24) utilizando análise através de *phantom* demonstrou que a angiotomografia quantifica melhor o grau de estenose do lúmen coronariano do que a cinecoronariografia em casos de lúmens com a geometria não circular. Outros dois estudos demonstraram que, quando comparadas, a tomografia e a cinecoronariografia possuem um acurácia similar (25-26) na avaliação da estenose luminal correlacionada com a predição de alterações hemodinâmicas diagnosticadas pela análise da reserva de fluxo fracional (FFR). No entanto, esses estudos utilizaram um método semiquantitativo na identificação da estenose coronariana pela tomografia, possivelmente limitando a quantificação das alterações anatômicas correlacionadas com a restrição de fluxo coronariano.

Portanto, a tomografia computadorizada de múltiplos canais é um excelente método não invasivo para a avaliação e quantificação da DAC, porém, a sua correlação hemodinâmica com os métodos utilizados no manejo clínico dos pacientes portadores desta doença ainda requer maiores investigações.

1.5 Estudo Multicêntrico Internacional Core 64

O Core 64 foi um estudo prospectivo, multicêntrico envolvendo nove hospitais em sete países (3 hospitais nos Estados Unidos e 1 em cada um dos seguintes países: Brasil, Canadá, Singapura, Japão, Alemanha e Holanda). Nesse estudo, foi realizada uma avaliação das doenças arteriais coronarianas pela TCMD com 64 canais, com o objetivo de detectar lesões ateroscleróticas que levam à estenose coronariana, usando a cinecoronariografia como "padrão-ouro". Também foram realizados em um grupo de pacientes e anteriormente à tomografia, estudos de CPM. Todos os centros receberam aprovação dos seus respectivos comitês de ética locais assim como todos os pacientes assinaram um consentimento concordando com a realização do estudo. O projeto do Core 64 foi estruturado por um comitê interno e os patrocinadores desse projeto não estiveram envolvidos em nenhuma etapa do estudo como estruturação, aquisição, análises de dados e preparação do manuscrito.

1.6 Correlação entre TCMD com 64 Canais, Angiografia Convencional e CPM na Detecção da Doença Arterial Coronariana Isquêmica

Com o desenvolvimento de novos métodos diagnósticos não invasivos como a TCMD e a CPM, tornou-se possível a realização de um diagnóstico acurado das doenças obstrutivas arteriais coronarianas, sem muitas vezes, a necessidade da realização de procedimentos invasivos como a cinecoronariografia. Recentes publicações (19-20) avaliaram a acurácia da tomografia computadorizada de 64 canais de detectores na detecção de estenose coronariana usando a cinecoronariografia como método de referência, e revelaram altos valores de sensibilidade (85%-100%) e especificidade (90%-96%). Contudo, esses dois métodos diagnósticos, apesar de mostrarem alta acurácia na avaliação anatômica da estenose coronariana, deixam a desejar quanto à quantificação do déficit perfusional miocárdico, não sendo possível ser feita uma adequada correlação anátomo-funcional da região isquêmica afetada pela obstrução arterial. A CPM é um método não invasivo que permite a detecção das doenças obstrutivas coronarianas (18). Além disso, possibilita a avaliação funcional em nível celular do território afetado, trazendo importantes informações na estratificação de risco do paciente (27). Desse modo, neste estudo procurou-se utilizar dados do estudo multicêntrico Core 64 para comparar a acurácia da tomografia computadorizada de 64 canais de detectores, da angiografia convencional e da CPM na detecção da DAC isquêmica, assim como definir a correlação anátomo-funcional entre os três métodos.

Sendo assim, o presente estudo compara métodos não invasivos (TCMD e CPM) com um método invasivo (cinecoronariografia) na detecção da DAC. A tendência da medicina moderna é realizar diagnósticos de uma forma cada vez menos invasiva, proporcionando assim, menores riscos relativos ao procedimento, aumento da eficiência terapêutica pelo diagnóstico precoce da DAC e um melhor manejo clínico dos pacientes portadores dessa doença.

1.7 Perspectivas futuras no diagnóstico da doença arterial coronariana isquêmica

Durante as últimas décadas houve uma rápida evolução no diagnóstico da DAC. Com o advento da TCMD na primeira década do século XXI, tornou-se possível, pela primeira vez na medicina, a realização de um diagnóstico anatômico não invasivo e acurado dessa doença. Nos anos subsequentes, com o aperfeiçoamento tecnológico através do incremento das resoluções espacial e temporal na aquisição das imagens, foi possível realizar um diagnóstico que vai além da mera luminologia. Agora, além de quantificar o grau de redução da luz das artérias, é possível fazer uma análise dos componentes das placas ateroscleróticas que causam obstrução das coronárias levando a isquemia. Em paralelo, métodos diagnósticos já consagrados em relação à análise funcional, como a CPM e o ecocardiograma de *stress*, reforçavam cada vez mais a sua importância na prática clínica como diagnóstico complementar à avaliação anatômica, possibilitando-se, dessa forma, avaliar a repercussão hemodinâmica da obstrução coronariana evidenciada pela tomografia computadorizada ou pela cinecoronariografia. No entanto, como foi demonstrado neste estudo, os métodos anatômicos e funcionais apesar de serem complementares no diagnóstico da DAC trazendo importantes informações clínicas, possuem uma acurácia apenas moderada quando utilizados em conjunto para avaliar a repercussão anatomo-funcional da lesão coronariana. Como tentativa de aumentar a acurácia diagnóstica desenvolveu-se nos últimos anos novos métodos que visam a realizar o diagnóstico anátomo-funcional acurado das lesões em um único exame. O estudo da perfusão miocárdica feito pela própria tomografia computadorizada vem sendo uma das grandes promessas em relação a esta nova perspectiva. Um recente estudo publicado por Rochite et al (28), revela que a adição da perfusão miocárdica ao protocolo de tomografia coronariana aumenta a acurácia do método na detecção da relevância hemodinâmica da lesão. Um outro método promissor que vem sendo cada vez mais utilizado em diversas partes do mundo é o PET-CT. Di Carli et al (29) demonstraram através de uma revisão da literatura que a utilização dessa tecnologia revela-se muito promissora no diagnóstico da relevância isquêmica das lesões obstrutivas através da análise da perfusão e do metabolismo miocárdicos, vindo a ser uma das grandes promessas na avaliação anátomo-funcional da DAC. Finalmente, uma nova tecnologia revelada recentemente, o Fluxo de Reserva Fraccional (FFR) vem a ser outra grande promessa na busca do diagnóstico anátomo-funcional realizado pela tomografia cardíaca. Um estudo publicado por Min e Berman et al (30) revelou que, comparado ao diagnóstico anatômico usual realizado através da tomografia coronariana , a adição do FFR ao exame possibilita um aumento de duas vezes na sua acurácia na detecção da relevância isquêmica de lesões causando estenoses coronarianas moderadas.

Novas tecnologias e estudos continuam a ser desenvolvidos visando realizar um diagnóstico cada vez menos invasivo e acurado da doença arterial coronariana isquêmica, possibilitando dessa forma, a prevenção de uma das maiores causas de morte nos países desenvolvidos.

2. OBJETIVOS

2.1 Avaliar a sensibilidade e a especificidade da angiotomografia e da cinecoronariografia para identificar pacientes com isquemia miocárdica detectada pela cintilografia de perfusão miocárdica.

2.2 Comparar a análise quantitativa da angiotomografia com a da cinecoronariografia na identificação de pacientes com anormalidades perfusionais demonstradas pela cintilografia de perfusão miocárdica.

2.3 Avaliar a correlação anátomo-funcional entre os diferentes métodos de imagem.

3. ARTIGO CIENTÍFICO PUBLICADO

ORIGINAL ARTICLE

Quantitative coronary arterial stenosis assessment by multidetector CT and invasive coronary angiography for identifying patients with myocardial perfusion abnormalities

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Background. **Semi-quantitative stenosis assessment by coronary CT angiography only modestly predicts stress-induced myocardial perfusion abnormalities. The performance of quantitative CT angiography (QCTA) for identifying patients with myocardial perfusion defects remains unclear.**

Methods. **CorE-64 is a multicenter, international study to assess the accuracy of 64-slice QCTA for detecting ≥50% coronary arterial stenoses by quantitative coronary angiography (QCA). Patients referred for cardiac catheterization with suspected or known coronary artery disease were enrolled. Area under the receiver-operating-characteristic curve (AUC) was used to evaluate the diagnostic accuracy of the most severe coronary artery stenosis in a subset of 63 patients assessed by QCTA and QCA for detecting myocardial perfusion abnormalities on exercise or pharmacologic stress SPECT.**

Results. **Diagnostic accuracy of QCTA for identifying patients with myocardial perfusion abnormalities by SPECT revealed an AUC of 0.71, compared to 0.72 by QCA (P = .75). AUC did not improve after excluding studies with fixed myocardial perfusion abnormalities and total coronary arterial occlusions. Optimal stenosis threshold for QCTA was 43% yielding a sensitivity of 0.81 and specificity of 0.50, respectively, compared to 0.75 and 0.69 by QCA at a threshold of 59%. Sensitivity and specificity of QCTA to identify patients with both obstructive lesions and myocardial perfusion defects were 0.94 and 0.77, respectively.**

Conclusions. **Coronary artery stenosis assessment by QCTA or QCA only modestly predicts the presence and the absence of myocardial perfusion abnormalities by SPECT. Confounding variables affecting the relationship between coronary anatomy and myocardial perfusion likely account for some of the observed discrepancies between coronary angiography and SPECT results. (J Nucl Cardiol 2012)**

Key Words: CT angiography • SPECT • myocardial ischemia • cardiac computed tomography

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INTRODUCTION

CT coronary angiography accurately identifies patients with obstructive coronary artery disease (CAD).[1] Since percutaneous coronary intervention appears to be most beneficial in hemodynamically significant coronary arterial stenoses, identifying such lesions as opposed to merely obstructive stenoses may be more desirable.[2] If anatomic assessment of atherosclerotic lesions is capable of predicting hemodynamic significance remains controversial. In support of this notion, intravascular ultrasound (IVUS) assessment of lumen obstruction correlates well with hemodynamic evaluation by coronary flow reserve.[3] Conventional quantitative coronary angiography (QCA), on the other hand, correlates poorly with fractional flow reserve (FFR) possibly because of its known limitations in accurately assessing complex lumen geometry.[4-7] CT angiography shares some of the favorable features of IVUS, i.e., allowing cross-sectional lumen analysis, and thus, may be similarly positioned to accurately assess luminal dimensions. Indeed when compared to IVUS, lumen area measurements by CT agreed better than those by QCA.[8] We recently showed that CT angiography more accurately quantifies lumen diameter stenosis than QCA in phantom vessels with non-circular geometry.[9] Yet in two studies, CT assessment of lumen stenoses was not more accurate than QCA in predicting hemodynamic significance by FFR.[10,11] These investigations, however, were conducted using semi-quantitative CT stenosis assessment possibly limiting the identification of an anatomical threshold that best predicts blood flow restriction. Accordingly, the purpose of this study was to use *quantitative* CT angiography (QCTA) for coronary artery stenosis assessment in comparison to QCA for identifying patients with myocardial perfusion abnormalities.

METHODS

Study Design

The Coronary Artery Evaluation Using 64-Row (CorE-64) Multi-Detector Computed Tomography Angiography study is a prospective, multicenter study performed at nine hospitals in seven countries to evaluate the diagnostic accuracy of QCTA for detecting coronary artery stenoses in patients with suspected obstructive CAD.[12] All centers received study approval from their local institutional review boards, and all patients gave written informed consent. In a subset of 63 patients, clinically driven myocardial stress perfusion studies were performed prior to CTA and conventional coronary angiography, which represents the study population for this investigation.

Patient Population

The patient population of the CorE-64 international study has been described in detail elsewhere.[12] In brief, 405 study participants were selected for the study according to the following criteria: patients who are at least 40 years of age, with symptoms of relevant CAD and indication for conventional coronary angiography. Patients were not eligible if they had history of cardiac surgery, allergy to iodinated contrast or contrast induced nephropathy, multiple myeloma, organ transplantation, renal insufficiency, atrial fibrillation, New York Heart Association class III or IV heart failure, aortic stenosis, percutaneous coronary intervention within the past 6 months, intolerance to beta-blockers, or a body-mass index of more than 40. Patients with Agatston calcium scores of 600 or greater were prespecified to be excluded from the primary analysis of the CorE-64 study but were included for secondary analyses performed identically to the main cohort. Thus, in contrast to the main study cohort, patients with calcium score of 600 and greater were included in this investigation. Of the entire CorE-64 cohort, the patient population for this investigation consists of 63 patients who underwent clinically driven nuclear stress perfusion imaging prior to CT imaging.

Image Acquisition and Data Analysis by 64-Row CTA

Methods applied in the CorE-64 study have been described in detail elsewhere.[12] In brief, patients underwent two multidetector CT tests (coronary calcium scoring and angiography) using 64-row scanners with a slice thickness of 0.5 mm (Aquilion, Toshiba Medical Systems). Calcium scoring was performed with the use of prospective electrocardiographic (ECG) gating with 400 milliseconds gantry rotation, 120-kV tube voltage, and 300-mA tube current. Total calcium score was determined by the Agatston method. For CT angiography, retrospective ECG gating was used, with heart rate-adjusted gantry rotations of 350-500 ms to enable adaptive multisegmented reconstruction. Sublingual nitrates were given before CT angiography. Iopamidol (Isovue 370, Bracco Diagnostics) was the intravenous contrast medium used for this study. Beta-blockers were given if the resting heart rate was above 70 beats per minute. Raw image data sets from all acquisitions were analyzed by an independent core laboratory. Using a modified 29- to 19-segment reduced coronary artery segmentation,[12] two experienced independent observers, who were blinded to all clinical and stress testing findings, visually assessed each of 19 non-stented segments that were 1.5 mm or more in diameter, for the presence of a stenosis of 30% or greater. Then, segments with at least one visible stenosis of 30% or more were manually quantified with the use of commercially available software (Vitrea2 version 3.9.0.1, Vital Images). For this purpose, readers used electronic calipers and/or semi-automatic coronary artery lumen contour detection (Sureplaque from Vital Images) (Figure 1) for identifying the minimum lumen diameter and proximal and distal disease-free reference sites for each lumen stenosis.[13,14] Both the caliper tool and the semi-automatic arterial contour detection algorithms were used in longitudinal as well as cross-sectional projections at the discretion of the readers. Resultant percent diameter stenoses were averaged for the two readers. Inter-reader visual and quantitative differences exceeding 50% were resolved by a third observer.

Image Acquisition and Data Analysis by Conventional Coronary Angiography

Conventional coronary angiography was performed no later than 30 days after CT angiography using conventional techniques of QCA. All coronary segments with 1.5 mm or more in diameter were analyzed visually and quantitatively using the classification of a 29-segment standard model[15] which was condensed to 19 segments for the equivalence of the number of coronary segments used in evaluation by CT.

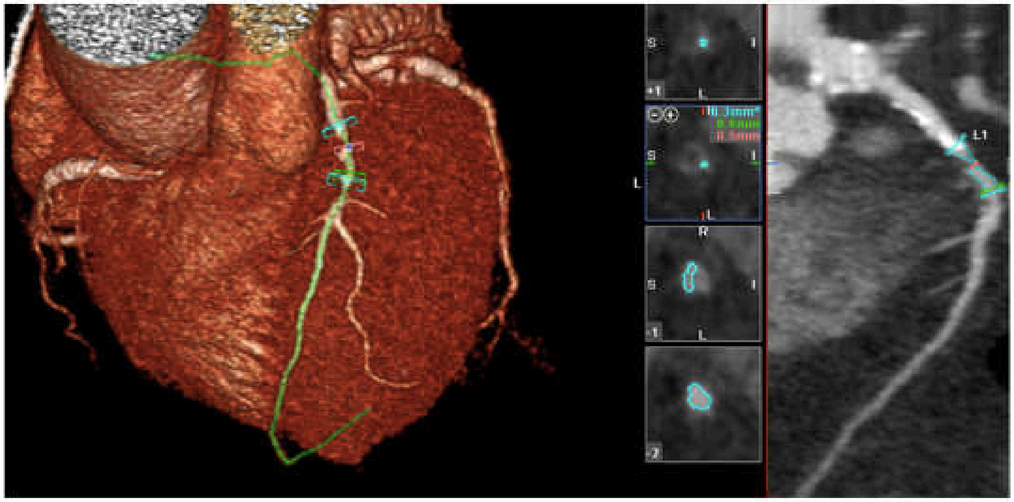

Figure 1. Example of coronary arterial lumen stenosis quantification by QCTA with the aid of semi-automated lumen contour detection (Sureplaque, Vital Images). On the left side, a three-dimensional reconstruction of the heart is seen with the coronary artery stenosis indicated in the mid-portion of the left anterior descending coronary artery. On the right side, cross-sectional and longitudinal images of curved multiplanar reformations are shown, demonstrating contour tracing of a severe (82%) lumen stenosis.

Evaluation by QCA was performed by two experienced readers blinded to the results of CT and SPECT using the software (CAAS II version 2.0.1 Research QCA, Pie Medical Imaging) in all coronary segments revealing diameter stenoses of 30% or greater by visual inspection.

Image Acquisition and Data Analysis by Myocardial Perfusion Imaging (SPECT)

All SPECT studies were performed and interpreted at the CorE-64 study sites according to the standards recommended by the American Society of Nuclear Cardiology.[16] Myocardial perfusion imaging studies were performed using 1- or 2-day protocols with either pharmacological agents (dipyridamole, adenosine, or dobutamine) or exercise stress. The radiotracers utilized were 99mTc-sestamibi, 99mTc-tetrofosmin, and thallium-201 at doses from 2 to 3 mCi for thallium-201, 7 to 10 mCi for 99mTc-sestamibi or 99mTc-tetrofosmin at rest and about three times more (21 to 30 mCi) of radiotracers in the last stress stage. Only one patient underwent myocardial perfusion using a dual-isotope protocol with the intravenous administration of thallium-201 during rest and 99mTc-setamibi during the stress stage. Standard perfusion stages of rest and stress were performed at baseline and with exercise or pharmacological stress. Myocardial perfusion was visually evaluated by the attending physician at the study sites. Assessment for myocardial perfusion abnormalities was performed based on the intensity of tracer uptake compared to a normal reference segment and based on the size of the affected myocardium area in relation to the entire myocardium. Perfusion abnormalities were graded for size and intensity as mild, moderate, and large and allocated to a myocardial region as recommended by the American Society of Cardiology.[16] Validated myocardial perfusion quantitation software, e.g., QPS (Cedars-Sinai Medical Center, Los Angeles, CA) was used at the discretion of the attending physician at study sites. A perfusion defect was defined as reversible if the change in regional activity was not evident on rest images. Results were sent to the CorE-64 core laboratory for analysis and comparison with QCTA and QCA.

Statistical Analysis

Statistical analyses were performed with Stata Statistical Software (Release 10.0, Stata Corporation, College Station, TX, 2007). To evaluate the diagnostic performance of coronary artery stenosis assessment by QCTA for identifying patients with myocardial perfusion defects (reference standard), we performed a patient-based receiver-operating-characteristic (ROC) curve as the measure of diagnostic accuracy. ROC analysis was applied to compare the diagnostic performance of QCTA and conventional angiography (using the threshold for significant coronary stenoses as the variable parameter) for identifying patients with perfusion defects by comparing the respective areas under the ROC curve (AUCs). Optimal performance was defined as diagnostic accuracy that yielded a balance of high sensitivity *and* specificity for a given threshold. Univariable logistic regression analysis was used to compare the findings from QCTA and QCA with the

Table 1. Patient characteristics

Age-mean (SD)	62.3 ± 9.2
Gender	
Female (%)	21 (13/63)
Male (%)	79 (50/63)
Smoking (%)	
Current	5 (03/63)
Former	49 (31/63)
Never	46 (29/63)
Body Mass Index (%)	
<25	27 (17/63)
25-30	38 (24/63)
30-39	32 (20/63)
40	3 (02/63)
Hypertension (%)	73 (46/63)
Dyslipidemia (%)	79 (50/63)
Family history of premature CAD (%)	33 (21/63)
Diabetes mellitus	30 (19/63)
Previous MI	20 (13/63)
SPECT exam parameters	
Exercise stress (%)	75 (47/63)
Pharmacological stress (%)	25 (16/63)

Data presented as mean ± standard deviation (SD) or percentage.
CAD, Coronary artery disease.

myocardial perfusion imaging results. The regression results are presented as odds ratios and their respective 95% CIs. All tests were two-tailed, the significance threshold was $P < .05$, and confidence intervals were 95%.

RESULTS

Patient Characteristics

The demographic characteristics of the study population are presented in Table 1. The mean age of the participants was 62.3 (±9.2) years and 79% were men. SPECT studies were performed using exercise stress in 75% of the participants while the remaining 25% received pharmacological stress/vasodilators. Fourteen of the 63 study subjects had a calcium score of 600 or greater. The median calcium score was 221 (interquartile range 36-478). The flow chart of patient enrollment and results is presented in Figure 2.

Diagnostic Accuracy of QCTA for Detecting Myocardial Perfusion Defects Using Predefined Stenosis Thresholds

Table 2 describes the diagnostic accuracy of coronary artery stenosis assessment by QCTA to identify

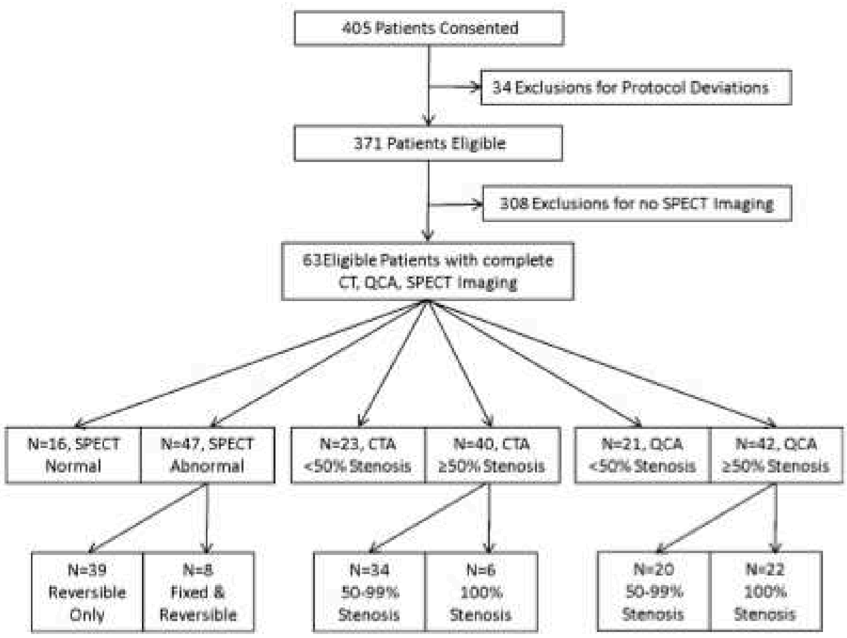

Figure 2. Flow chart of patient enrollment and results.

Table 2. Diagnostic accuracy of QCTA for identifying patients with any perfusion defects by SPECT

Stenosis thresholds	CTA-30%	CTA-40%	CTA-50%	CTA-60%	CTA-70%	CTA-80%
Sensitivity	87.2	83.0	70.2	66.0	51.1	36.2
Specificity	37.5	43.8	56.3	68.8	81.3	87.5
PLR	1.40	1.48	1.60	2.11	2.72	2.89
NLR	0.34	0.39	0.53	0.50	0.60	0.73
PPV	80.4	81.3	82.5	86.1	88.9	89.5
NPV	50.0	46.7	39.1	40.7	36.1	31.8

Disease prevalence by SPECT was 74.6%.
QCA, Quantitative coronary angiography; *QCTA*, quantitative CT angiography; *PLR*, positive likelihood ratio; *NLR*, negative likelihood ratio; *PPV*, positive predictive value; *NPV*, negative predictive value.

Table 3. Diagnostic accuracy of QCA and QCTA for identifying patients with only reversible perfusion defects by SPECT

Stenosis thresholds	QCA-50%	QCA-70%	CT-50%	CT-70%
Sensitivity	74.4	66.7	71.8	56.4
Specificity	45.8	54.2	50.0	79.2
PLR	1.37	1.45	1.44	2.71
NLR	0.56	0.62	0.56	0.55
PPV	69.0	70.3	70.0	81.5
NPV	52.4	50.0	52.2	52.8

Disease prevalence by SPECT was 61.9%.
QCA, Quantitative coronary angiography; *QCTA*, quantitative CT angiography; *PLR*, positive likelihood ratio; *NLR*, negative likelihood ratio; *PPV*, positive predictive value; *NPV*, negative predictive value.

patients with any myocardial perfusion defects by SPECT. For a stenosis of ≥50% by QCTA, sensitivity and specificity to identify patients with SPECT perfusion defects were 70.2 and 56.3%. The positive predictive values (PPV) and negative predictive values (NPV) were 82.5 and 39.1%, respectively. For a 70% stenosis threshold by QCTA, sensitivity, specificity, PPV, and NPV were 51.1, 81.3, 88.9, and 36.1%, respectively. Considering only reversible defects (disease prevalence 61.9%), sensitivity, specificity, PPV, and NPV at 50 and 70% thresholds by QCTA were 71.8, 50.0, 70.0, 52.2% and 56.4, 79.2, 81.5, 52.8% respectively (Table 3).

Diagnostic Accuracy of QCA for Detecting Myocardial Perfusion Defects Using Predefined Stenosis Thresholds

Table 4 presents the diagnostic accuracy of coronary artery stenosis assessment by QCA for identifying patients with myocardial perfusion defects by SPECT. For a 50% stenosis threshold, sensitivity, specificity, PPV, and NPV were 74.5, 56.3, 83.3, and 42.9%. For a 70% threshold, sensitivity, specificity, PPV, and NPV for QCA were 68.1, 68.8, 86.5, and 42.3%. For only reversible defects (Table 3), sensitivity, specificity, PPV, and NPV at 50% QCA threshold were 74.4, 45.8, 69.0, and 52.4% and at 70% QCA threshold, sensitivity, specificity, PPV, and NPV were 66.7, 54.2, 70.3, and 50.0% .

Quantitative Stenosis Assessment by QCA and QCTA for Identifying Patients with Myocardial Perfusion Abnormalities

Accuracy of quantitative coronary artery stenosis assessment by QCTA and QCA for identifying patients with myocardial perfusion defects by SPECT are presented in Figure 3. Area under the ROC curve was 0.71 (0.54-0.87) for QCTA and for QCA was 0.72 (0.59-0.87) ($P = .75$). Optimal diagnostic accuracy for QCTA was found at a stenosis threshold of 43% yielding a

Table 4. Diagnostic accuracy of QCA for identifying patients with any perfusion defects by SPECT

Stenosis thresholds	QCA-30%	QCA-40%	QCA-50%	QCA-60%	QCA-70%	QCA-80%
Prevalence	74.6	74.6	74.6	74.6	74.6	74.6
Sensitivity	85.1	76.6	74.5	72.3	68.1	59.6
Specificity	25.0	56.3	56.3	68.8	68.8	75.0
PLR	1.13	1.75	1.70	2.31	2.18	2.38
NLR	0.60	0.42	0.45	0.40	0.46	0.54
PPV	76.9	83.7	83.3	87.2	86.5	87.5
NPV	36.4	45.0	42.9	45.8	42.3	38.7

Disease prevalence by SPECT was 74.6%.
QCA, Quantitative coronary angiography; *PLR*, positive likelihood ratio; *NLR*, negative likelihood ratio; *PPV*, positive predictive value; *NPV*, negative predictive value.

sensitivity of 81% and a specificity of 50%. Optimal stenosis threshold for QCA was found at 59% yielding a sensitivity of 75% and a specificity of 69%. Considering only reversible SPECT defects, there were no significant differences for QCTA and QCA diagnostic accuracies (0.66 vs 0.67; $P = .8$; Figure 3B). Diagnostic accuracy of QCTA and QCA for detecting any versus only reversible myocardial perfusion defects after excluding patients with total coronary artery occlusions did not significantly change compared to overall results (Table 5). Figure 4A shows the results of logistic regression of coronary artery stenosis assessment by QCTA and QCA versus perfusions defects by SPECT. For every percent increment in coronary artery stenosis by either QCTA or QCA, the odds of a perfusion defect increased by 3% ($P < .05$). Similar results were seen for reversible defects (Figure 4B).

Diagnostic Accuracy of QCTA to Identify Patients with a Combined Myocardial Perfusion Defect and ≥50% Stenosis by QCA

Sensitivity, specificity, PPV, and NPV for QCTA (50% stenosis threshold) to identify patients with both myocardial perfusion abnormality by SPECT and ≥50% coronary arterial stenosis by QCA were 94, 77, 81, 91%, respectively. Using a lower stenosis threshold (40%)—as commonly done in clinical practice as gatekeeper for invasive angiography—sensitivity, specificity, PPV, and NPV were 97, 54, 75, and 93%, respectively.

DISCUSSION

We found similar modest accuracy for quantitative coronary arterial stenosis assessment by QCTA and QCA for identifying patients with myocardial perfusion defects by SPECT. Using coronary arterial stenosis thresholds ranging from 30 to 100% by either QCTA or QCA did not yield high accuracy for identifying patients with myocardial perfusion abnormalities by SPECT. Rather, in some instances, myocardial perfusion abnormalities were associated with lower grade arterial stenoses and in others they paired with higher grade lumen obstruction. The accuracy for either method did not increase when only reversible perfusion defects were considered or when patients with total coronary arterial occlusions were excluded from analysis. Importantly, however, the sensitivity of QCTA to identify patients with combined myocardial perfusion defects by SPECT and obstructive CAD by QCA was high.

The relationship between coronary arterial anatomy and blood flow restrictions causing myocardial ischemia is complex. Accordingly, a single stenosis threshold, e.g., 50 or 70% coronary arterial diameter stenosis, is unlikely to identify most patients with myocardial perfusion defects. In this investigation, we used quantitative coronary arterial stenosis measurements by QCTA to assess the relationship between coronary anatomy and myocardial ischemia over a wide range of stenoses (30-100%). However, compared to previous reports using semi-QCTA (e.g., using predefined visual stenosis thresholds of 25, 50% etc.) our results were similar, which may suggest that the application of QCTA does not confer an advantage over semi-quantitative, categorical assessment.[17-21] Our reported sensitivity and specificity for QCTA to identify patients with inducible ischemia by SPECT are similar to those reported by Hacker et al[19] On the other hand, Gaemperli et al[18] reported higher sensitivity, whereas Bauer et al[22] found lower sensitivity for identifying patients with myocardial perfusion defects by QCTA. Predictive values highly varied among studies as one would expect in patient populations with different disease prevalence.[1]

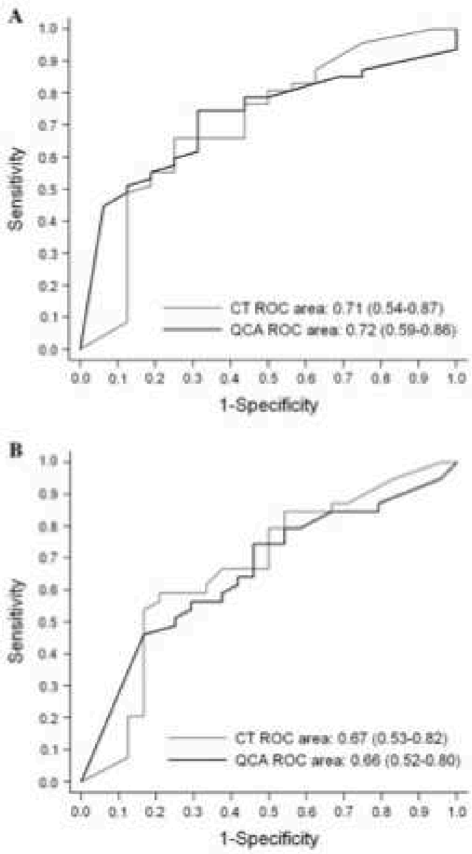

Figure 3. The ROC curves for the diagnostic accuracy of QCA and QCTA to identify patients with any myocardial perfusion defects by SPECT for all defects (n = 47, **A**) and reversible defects only (n = 39, **B**). There was no statistically significant difference between the areas under the respective ROC curves (*P* = .75 for all defects and .80 for reversible only).

Possible explanations for the modest performance of QCTA to predict myocardial perfusion defects may include its poorer spatial resolution compared to QCA. However, at least in phantom studies, QCTA appeared quite capable of accurate lumen quantification and in fact had greater accuracy for stenosis assessment in lumen with non-circular geometry.[9] Other explanations include the lack of prospective assessment, i.e., coronary artery lesions were assessed by QCTA with the intention to match QCA assessment and not to assess for hemodynamic significance. Finally, diameter stenosis was used in this study to determine lumen obstruction whereas luminal area assessment may be closer associated with hemodynamic significance.[23]

Besides technical factors, the modest association of anatomic assessment by either QCA or QCTA with functional assessment for the evaluation of CAD may also be explained by the complexity of factors leading to myocardial ischemia. In addition to the degree of luminal obstruction, the number of stenoses, extent of atherosclerotic plaque present, lesion length, extent of collateral flow, endothelial dysfunction, microvascular function, and possibly other factors and/or a combination of these influence the probability of myocardial ischemia.[24] In CorE-64, disease prevalence and morbidity were very high which increases the chance of microvascular dysfunction and perfusion defects even in the absence of flow-limiting stenoses, possibly explaining the relative high probability of ischemia even with lower degree stenoses (Figure 4). One may therefore argue it is unrealistic to expect high accuracy for simple arterial diameter stenosis measurements to predict a fairly complex outcome. The complexity of the matter may be further illustrated by the relationship between FFR and myocardial ischemia detected by SPECT. While the coronary blood flow characteristics assessed by FFR in the epicardial coronary artery is expected to predict myocardial ischemia even in the setting of collateral flow, several studies revealed a modest correlation between FFR and myocardial perfusion abnormalities in patients with multivessel disease.[25,26] Di Carli et al[27] have shown that even when utilizing a combination of anatomic and physiological assessment in a single method by PET-CT, the correlation of both CTA and PET-CT for predicting myocardial ischemia is poor. In contrast to many studies reporting overestimation of stenoses compared to QCA, we found no such trend in our study. Reasons for this discrepancy includes the use of quantitative as opposed to visual assessment—which is known to result in lower stenosis estimates[28]—as well as a conscious effort by CorE-64 readers not to overcall stenoses.[1]

STUDY LIMITATIONS

The primary objective of the CorE-64 study was to investigate the accuracy of 64-slice QCTA for detecting obstructive CAD compared to QCA. Since comparison with myocardial perfusion defects was not the primary goal, only a subset of patients underwent SPECT imaging, limiting this analysis. In contrast to QCTA and QCA protocols and analyses, no single protocol was followed for SPECT acquisition or was its analysis performed in an independent core laboratory. Indeed, SPECT results were likely to have influenced referral for

Table 5. Diagnostic accuracy of QCA and QCTA for identifying patients with perfusion defects by SPECT after exclusion of total coronary arterial occlusions

Stenosis thresholds	QCA-50%	QCA-70%	CT-50%	CT-70%
All defects				
Sensitivity	53.8	42.3	67.4	46.5
Specificity	60.0	73.3	64.3	92.9
PLR	1.35	1.59	1.89	6.51
NLR	0.77	0.79	0.51	0.58
PPV	70.0	73.3	85.3	95.2
NPV	42.9	42.3	39.1	36.1
Reversible defects only				
Sensitivity	52.4	38.1	69.4	52.8
Specificity	55.0	65.0	57.1	90.5
PLR	1.16	1.09	1.62	5.54
NLR	0.87	0.95	0.54	0.52
PPV	55.0	53.3	73.5	90.5
NPV	52.4	50.0	52.2	52.8

QCA, Quantitative coronary angiography; *QCTA*, quantitative CT angiography; *PLR*, positive likelihood ratio; *NLR*, negative likelihood ratio; *PPV*, positive predictive value; *NPV*, negative predictive value.

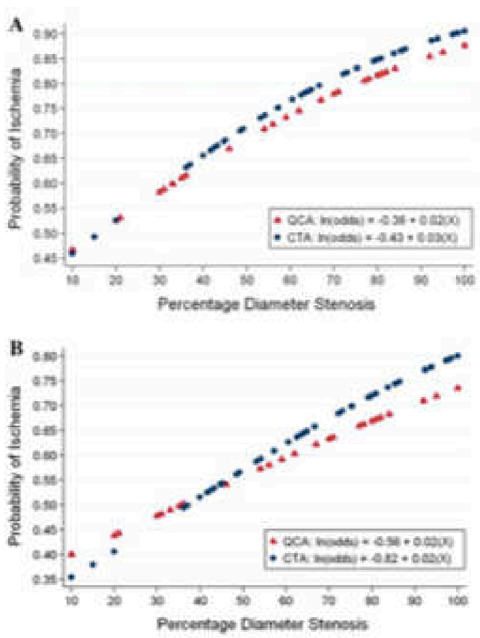

Figure 4. Probability of myocardial ischemia as a function of coronary arterial diameter stenoses by QCA and QCTA for all defects (n = 47, **A**) and reversible defects only (n = 39, **B**).

cardiac catheterization and study enrollment, and likely increased the probability of positive SPECT results among this cohort. Although myocardial perfusion imaging by SPECT is an accepted standard for assessing myocardial perfusion abnormalities in patients with known or suspected CAD, the technique only allows the detection of *relative* myocardial perfusion differences which particularly affects patients with multivessel or left main CAD. Finally, all analyses were based on patients but not on a vessel level, precluding conclusions on associations of lesion location and myocardial perfusion abnormalities. An analysis on a vessel level was not attempted because of the variability of the coronary arterial anatomy associated with myocardial perfusion territories.[29]

CONCLUSION

QCTA is no more accurate than QCA for identifying patients with myocardial perfusion defects by SPECT. While the probability of myocardial ischemia increases with the degree of diameter stenosis, the accuracy for QCTA or QCA for identifying patients with myocardial perfusion abnormalities is similarly modest. Given the complexity of factors involved leading to myocardial ischemia, simple arterial diameter measurements appear inadequate for accurate prediction of blood flow restrictions.

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4. CONCLUSÕES

4.1 Apesar de a probabilidade de isquemia miocárdica aumentar com o grau de estenose da artéria coronária, tanto a angiotomografia como a cinecoronariografia apresentam sensibilidade e especificidade apenas moderadas para prognosticar as alterações perfusionais detectadas pela CPM.

4.2 A acurácia da angiotomografia não é significativamente maior que a da cinecoronariografia para identificar pacientes com defeitos perfusionais demonstrados pela CPM.

4.3 Devido à complexidade dos fatores envolvidos na gênese da isquemia miocárdica, a simples medida do diâmetro da artéria coronária através de sua análise anatômica, parece ser inadequada para prever restrições ao fluxo sanguíneo arterial diagnosticadas através da CPM.

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