Evaluation of the efficacy of computed tomographic coronary angiography in assessing coronary artery morphology and physiology: rationale and study design

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Abstract

Computed tomographic coronary angiography (CTCA) is a non-invasive imaging modality which allows plaque burden and composition assessment and detection of plaque characteristics associated with increased vulnerability. In addition, CTCA-based coronary artery reconstruction enables local haemodynamic forces assessment, which regulate plaque formation and vascular inflammation and prediction of lesions that are likely to progress and cause events. However, the use of CTCA for vulnerable plaque detection in the clinical arena remains limited. To unlock the full potential of CTCA and enable its broad use, further work is needed to develop user-friendly processing tools that will allow fast and accurate analysis of CTCA, computational fluid dynamic modelling and evaluation of the local hemodynamic forces. The present study aims to develop a seamless platform that will overcome the limitations of CTCA and enable fast and accurate evaluation of plaque morphology and physiology. We will analyse imaging data from 70 patients with coronary artery disease who will undergo state-of-the-art CTCA and near infrared spectroscopy-intravascular ultrasound imaging, develop and train algorithms that will take advantage the intravascular imaging data to optimise vessel segmentation and plaque characterization and will design an advanced module that will enable reconstruction of coronary artery anatomy from CTCA, blood flow simulation shear stress estimation and comprehensive visualization of vessel pathophysiology. These advances are expected to facilitate the broad use of CTCA not only for risk stratification but also for the evaluation of the effect of emerging therapies on atherosclerotic evolution.

Introduction

There is growing evidence that vessel physiology and plaque characteristics are able to detect high-risk plaques that are likely to cause in the future cardiovascular events.[1-4] Accurate *in vivo* assessment of plaque characteristics is traditionally performed by intravascular imaging. Today, three intravascular imaging modalities are available in the clinical arena [intravascular ultrasound (IVUS), optical coherence tomography (OCT), and near infrared spectroscopy (NIRS)-IVUS] that have been tested in prospective large scale studies and showed that they can provide useful prognostic information and detect vulnerable lesions and high-risk patients that are likely to suffer a cardiovascular event.[1-3,5] Histology studies have shown that NIRS-IVUS is today the best technique for assessing plaque phenotype and characterising its composition as it combines an ultrasound probe that gives information about plaque and calcific tissue burden and a NIRS probe that can accurately detect lipid component.[6,7] Despite the potential of this modality in detecting vulnerable plaques its use in the clinical arena for this purposes is limited as it is an invasive technique - and thus it can be used only in patients undergoing coronary angiography - is associated with a risk of complications and it does not allow complete assessment of the entire coronary tree.

Non-invasive imaging and in particular computed tomographic coronary angiography (CTCA) have appeared as a promising alternative for the study of atherosclerosis and seems to be able to overcome limitations of intravascular imaging. Cumulative evidence has shown that CTCA can detect lumen and vessel wall dimensions and quantify plaque burden and composition.[8-11] Moreover, recent reports have shown that computational fluid dynamic analysis is feasible in CTCA-derived reconstructions and that the estimated local hemodynamic forces have a value in detecting segments that are likely to exhibit disease progression.[12-14] In addition, large scale retrospective studies have shown that CTCA can identify vulnerable plaques and patients at risk of suffering cardiovascular events while recently the EMERALD study have demonstrated that plaque characteristics and the local hemodynamic forces estimated by CTCA has an incremental value in differentiating lesions that caused a myocardial infarction from these that remained quiescent.[15] Despite these promising findings, CTCA is not used in everyday clinical practice for vulnerable plaque detection and patient risk stratification. This at least

partially should be attributed to the increased time required for CTCA analysis as well as to the limitations of CTCA to accurately detect lumen and vessel wall borders and quantify plaque burden and composition – especially in calcified plaques. In the present study, we aim to develop and validate methodologies that will overcome the above limitations and enable the broad use of CTCA for accurate risk stratification and thus personalised secondary prevention.

Study design

Study objectives

The "Evaluation of the efficacy of computed tomographic coronary angiography in assessing coronary artery morphology and physiology" is a prospective single arm multi-imaging single centre study. The primary objective of the study is to examine whether CTCA allows accurate assessment of coronary artery plaque phenotype using invasive imaging as gold standard. Secondary objectives of the study are: 1) to develop segmentation algorithms and plaque characterisation methodologies that will enable accurate assessment of plaque burden and composition, 2) examine the efficacy of CTCA in assessing the local haemodynamic forces and 3) develop a seamless platform that will enable CTCA segmentation, plaque characterisation, blood flow simulation and evaluation of the ESS in less than 1 ½ hour per patient.

Patient population

Seventy patients with typical angina symptoms who had elective coronary angiography showing at least one obstructive lesion and are referred to Barts Heart Centre for further evaluation with a fractional flow reserve (FFR) study or percutaneous coronary intervention (PCI) will be considered for participation. The inclusion and exclusion criteria of the study are shown in Table 1. Patients who fulfil these criteria will be contacted by the research team and a copy of the patient information sheet will be provided. Patients who are keen to participate will be booked to attend two visits to the Barts Heart Centre – 1) study consenting followed by CTCA and pre-assessment clinic visit and 2) 3-vessel intravascular imaging study along with their clinical treatment as required. Following the procedure,

patients will be transferred back to the day case ward for monitoring and they will be discharged later that day.

Patient withdrawal

Patients will be free to withdraw consent at their own request at any time without the need to provide reasons for their decisions. Additionally, the principal investigator will be able to withdraw a patient from the study if there are concerns about patient safety and well-being. Withdrawals will be documented in the case report form and in the patients' medical records.

Patient pre-assessment

On the day of pre-assessment visit, patient's fitness for invasive angiography will be assessed by trained nurses as per Barts Health NHS Trust protocols. Blood samples (20mls) will be obtained to check for full blood count, renal function and lipid profile. Patients cardiovascular risk factors, revascularisation history and current medications will be recorded.

CTCA

CTCA will be performed after consenting using a third generation dual-source scanner (Somatom Force, Siemens Healthineers, Forchheim, Germany). Before the CT scan all patients will receive sublingual nitroglycerin (0.4 mg/dose) and those with heart rate >70 beats per minute, will also receive intravenous metoprolol (maximum 40 mg), provided there are no contraindications. The CTCA scan parameters include prospective ECG-triggered sequential scan mode, gantry rotation time of 250ms, 128x2x0.5mm collimation with z-flying focal spot for both detectors, minimum tube voltage of 100kV and tube current determined by the scanner. A bolus of iodinated contrast agent (Omnipaque 350) which varies between 65 or 78mls depending on the patient's body habitus will be injected intravenously at an injection rate of 4-5ml/s followed by 32 mls saline chaser with the same injection rate. A test bolus technique will be used to synchronise the start of image acquisition. All CT images will be reconstructed with a variety of different slice thickness, convolutional kernels and iterative reconstructions techniques and will be stored digitally for offline analysis.

Intravascular imaging

A senior interventional trainee and consultant cardiologist will perform the coronary angiography according to Barts Health Trust protocols. The access route, choice of guide catheters and coronary wires will be left to the operators' discretion. Heparin (intracoronary or intravenous according to the operator's discretion) will be administered to maintain an ACT>250 throughout the procedure. All patients receive 400 micrograms of intracoronary nitrate prior to image acquisition, provided there are no contraindications. Images will be acquired with good contrast opacification and minimal vessel overlapping. Before FFR or PCI – depending on the clinical need - NIRS-IVUS imaging will be performed in the epicardial vessels and their major side branches. NIRS-IVUS will be performed by the Makoto™ imaging system (Infraredx, Burlington, MA) The catheter will be advanced 5mm distally to the most distal side branch that is visible in both angiography and CTCA imaging and will be pulled-back by a motorised pullback device that will withdraw the catheter at 0.5mm/s; images will be acquired at 30 frames per second and digitally archived. Patients will then undergo FFR study or PCI as per clinical indication.

Image segmentation

Imaging data will be anonymised and analysed offline blinded to clinical details by an expert analysts using dedicated workstation. Anatomical landmarks (i.e., side branches) identified in the CTCA and NIRS-IVUS imaging data will be used to define segments of interest – i.e., segments that have been assessed by both imaging modalities. CTCA analysis will be performed by an expert analysist using the QAngioCT 2.1 Research Edition software that enables automated extraction of the luminal centreline, semi-automated detection of the lumen and outer vessel wall borders and quantification of the plaque burden and composition. NIRS-IVUS analysis will be performed by an operator with expertise in intravascular image analysis blinded to the CTCA analysis using dedicated software (QIvus 3.1, Medis Medical Imaging Systems, Leiden, The Netherlands). Lumen and outer vessel wall border detection will be performed in end-diastolic IVUS images while the presence of lipid component will be derived by the NIRS data that are displayed in colour coded map called chemogram (yellow indicates increased

probability and red low probability of lipid tissue). A metric of the lipid burden is the lipid core burden index (LCBI) which is computed as the fraction of the yellow pixels that correspond to lipid component divided by 1000. In addition, for each 2mm segments the block chemogram is generated that provides a summary of the chemogram for this segment. The NIRS and IVUS imaging data will be used to characterise plaque composition and its phenotype.

Vessel reconstruction, blood flow simulation and local haemodynamic forces assessment

CTCA coronary artery reconstruction will be performed using a module that automatically places the CTCA borders onto the luminal centreline and creates three dimensional (3D) surfaces of the lumen and outer vessel wall that can be processed with computational fluid dynamic (CFD) techniques.[13] The segment of interest and its side branches will be reconstructed using this approach and blood flow simulation will be performed using a module that will be incorporated into the QAngioCT software. An established and well validated methodology that relies on the fusion of NIRS-IVUS and the angiographic data will be used to reconstruct the segment of interest and its side branches (diameter >1mm) and in the obtained geometries blood flow simulation will be performed using identical boundary conditions with the CTCA-CFD analysis and the ESS distribution will be estimated.[16] (Figure 1).

Data post-processing

We anticipate NIRS-IVUS imaging to be performed on average in 2.5 vessels per patient; from these 40 will be randomly selected and used to train algorithms for CTCA segmentation and plaque characterisation (training dataset) while the remaining data will be used for validation purposes (validation dataset). In the training set, the segments of interest will be divided in 2mm segments and corresponding 2mm segments will be identified in the CTCA and NIRS-IVUS models. In each segment the following metrics will be estimated in NIRS-IVUS: mean lumen area, vessel wall area, plaque area and burden, mean calcific area, the LCBI and the predominant ESS. In addition, each segment will be classified as lipid-rich or non-lipid rich according to the block chemogram.[17] Similarly, in the CTCA models the mean lumen area, outer vessel wall area, plaque area, plaque burden, calcific area and the

mean predominant ESS will be estimated for every 2mm segment and compared with the estimations of NIRS-IVUS. Several approaches will be tested to optimise the segmentation of the lumen and vessel wall borders in CTCA including machine learning techniques and the best will be selected. The adaptive Hounsfield unit cut-offs that best identify lipid and calcific tissue will be defined and spread-out vessel plots portraying the distribution of the lipid tissue in the CTCA models will be created and compared with the output of NIRS. The block chemogram in NIRS-IVUS will be used to identify the 2mm CTCA derived lipid cut-off that enables accurate classification of the 2mm segments as lipid or non-lipid rich. The accuracy of these cut-offs will be tested in the validation dataset. In addition, in the validation dataset the NIRS-IVUS data will be used to identify coronary lesions – defined as segments with a plaque burden >40% in 3 consecutive frames.[18] For each lesion, its remodelling index, calcific and lipid component and plaque burden will be used to characterise their phenotype and classify them as: pathological intimal thickening/fibrotic plaques, fibro-calcific plaques, fibroatheromas, and calcified fibratheromas[7,19,20]The NIRS-IVUS lesion classification will be used as reference standard in order to assess the accuracy of CTCA in characterising lesion phenotype.

Power calculation and statistical analyses

The primary endpoint of the study is the ability of CTCA in detecting fibroatheromas. In the study of Garcia-Garcia et al that included 129 patients who underwent single vessel IVUS imaging,[18] 1.7 lesions were identified per patient. In the study of Puri et al. 45% of the detected lesions were classified as fibroatheromas based on histology.[7] In this study, a maximum 4mm LCBI >178, remodelling index > 1.1 and plaque burden >67% enabled detection of fibroatheromas with an excellent accuracy (c-index: 0.80). We anticipate that we will be able to perform NIRS-IVUS imaging in 2.5 coronary arteries per patient[21] and that CTCA imaging quality will be optimal in 93% of the studied patients.[22,23] Therefore, a sample size of 70 patients will allow us to study 162 vessels, of which 120 vessels will be used for validation (203 lesions, of which are 92 fibroatheromas) purposes. This dataset is anticipated to provide 80% power to demonstrate that CTCA has a similar sensitivity to NIRS-IVUS to detect fibroatheromas using the 5% significant level (AUC of CTCA 0.71-0.89 and assuming the true sensitivity of NIRS-IVUS is 0.80).

Secondary endpoints of the study are the accuracy of CTCA to identify: a) lipid-rich segments (using the block chemogram of NIRS-IVUS as gold standard), and b) segments exposed to low ESS (<1Pa, using the ESS estimated in the NIRS-IVUS based reconstructions as reference standard).

Correlation and liner regression analysis will be used to investigate the associations between mean lumen, outer vessel wall, plaque area, mean plaque burden and calcific tissue area estimated in the 2mm segments in the NIRS-IVUS and CTCA models and mixed models with random intercept and slope will be used to correct for patient effects.

Discussion

Cumulative evidence has demonstrated that plaque composition determines its vulnerability and enables more accurate risk stratification. Intravascular imaging studies have shown that even single vessel-plaque assessment provides useful prognostic information and identification of patients at risk.[3,5,24-26] Despite the increased cost and the risk of complications associated with intravascular imaging, this strategy may have a value in selected populations with a high cardiovascular risk such as the patients admitted with an acute coronary syndrome where the event rate at 1 year is as high as 20%. [27,28]

Modern submillimetre high resolution CTCA imaging allows non-invasive, complete assessment of the coronary tree and atherosclerotic plaques and offers a unique alternative in the study of atherosclerosis. Cumulative evidence has highlighted its value in assessing atheroma characteristics and identifying patients at risk for future events amongst individuals with no previous cardiac history, however its role in secondary prevention has not been explored at scale yet.[22,29,30] This at least partially should be attributed to the limited efficacy of the first generation CTCA scanners to assess complex atherosclerotic plaques and especially lesions with an increased calcific component and detect their phenotype, as well as to the increased time required to process the CTCA imaging data.[10,31,32]

The objective of this study is to take advantage of the advances in CTCA imaging and use hybrid intravascular imaging to overcome well-known limitations of CTCA by developing a novel platform that will incorporate efficient methodologies for automated and reliable processing of the CTCA imaging data, coronary reconstruction and blood flow simulation in less than 1 ½ hour. In contrast to other studies, we aim not only to validate but also train segmentation and plaque characterisation

algorithms and recognise and minimize the effect of common artefacts (i.e., calcium blooming artefact) on CTCA analysis, and thus assess more accurately plaque characteristics in patients with extensive/complex coronary artery disease. These advances will allow us to conduct studies that will examine the value of CTCA imaging in stratifying cardiovascular risk in patients with established coronary artery disease. This objective is timely as several new therapies that target vulnerable patients have been recently introduced in the clinical arena (i.e., Evolocumab, Alirocumab, prolonged dual antiplatelet treatment with low dose Ticagrelor),[33-35] while others have been tested in large clinical studies and are likely to have applications in the due course (i.e., Canakinumab)[36,37] and others are currently undergoing clinical evaluation [i.e., Colchicine (NCT02551094), Incliseran (NCT03705234)]. The above medications however have significant side effects or they are associated with an increased cost and thus they should be used only in well-defined high-risk patients. Unlocking the full potential of CTCA imaging in assessing atheroma characteristics and estimating the local hemodynamic forces – which in intravascular imaging studies appear to enable more accurate detection of vulnerable plaques and high-risk patients[38,39] – is essential for the broad use of this modality in the clinical arena for the identification of patients that are likely to sustain a cardiovascular event and benefit from an aggressive treatment of atherosclerosis.[40]

In addition, the platform that we hope to develop is expected to enhance the research applications of CTCA and facilitate the conduction of large clinical studies that will focus on the evaluation of the effect of new treatments on plaque growth. Moreover, this platform will enable assessment in large asymptomatic populations of the effects of the local hemodynamic forces on the formation and destabilization of vulnerable plaques, and of the interplay between plaque morphology and flow patterns and it is anticipated to broaden the applications of non-invasive fractional flow reserve in identifying flow limiting lesions.[41,42]

Ethical considerations

The study protocol has been approved by the local and independent Research Ethics Committee (REC reference: 17/SC/0566) and will be conducted in agreement with the Declaration of Helsinki. All the adverse events (AE) that are likely to occur during the study will be assessed for severity, causality,

seriousness and expectedness as per the sponsor's protocol; AE and serious adverse events (SAE) will be reported to the sponsor within five working days. If there is an increased event rate or concerns about patient safety during the conduction of the study, study termination will be considered.

Dissemination

We have recruited 50 patients to date. We aim to complete recruitment by late-2019 and publications will be prepared in the mid of 2020. Dissemination of the results will focus on publications in peer-reviewed journals in cardiovascular medicine and selected engineering journals as well as presentations at national and international meetings. The study has been also registered in a public registry (http://clinicaltrials.gov NCT035566440).

Sponsor

The sponsor of the study is University College London; the study is jointly funded by British Heart Foundation (PG/17/18/32883), University College London Biomedical Resource Centre (BRC492B) and Rosetrees Trust (A1773).

Summary

Despite the wealth of data supporting the use for CTCA for the assessment of coronary luminal stenosis, the application of this modality for plaque characterisation and risk stratification remains limited. In this study, we aim to use intravascular imaging and in particular, NIRS-IVUS to train and validate segmentation and plaque characterisation methodologies and incorporate reconstruction and blood flow simulation algorithms in a fast and user-friendly software that will enable the broad use of CTCA in the clinical arena for more accurate detection of high-risk patients and for the evaluation of the effect of emerging therapies on plaque progression.

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Table 1. Study inclusion and exclusion criteria

Inclusion criteria
1. Patients with stable angina that have at least one obstructive lesion on elective diagnostic coronary angiography that requires further assessment with intravascular imaging, invasive functional assessment or percutaneous coronary intervention
2. Age 18-75 years old
3. Patient is able and willing to provide their written consent
Exclusion criteria
1. History of previous coronary artery bypass graft surgery
2. History of heart failure New York Heart Association (NYHA) IV or severe left ventricular systolic dysfunction <30% regardless of patient symptom status
3. Documented allergy or inability to receive treatment with aspirin, heparin or thienopyridines
4. Patients that require surgical revascularisation following diagnostic angiogram
5. Renal impairment – estimated glomerular filtration rate of < 60 mL/min at screening.
6. History of acute coronary syndrome in the last 3 months
7. History of heart transplantation
8. Life expectancy of less than one year
9. Extensive coronary artery disease (i.e. multiple chronic total occlusions) or torturous coronary anatomy that does not allow assessment with NIRS-IVUS imaging

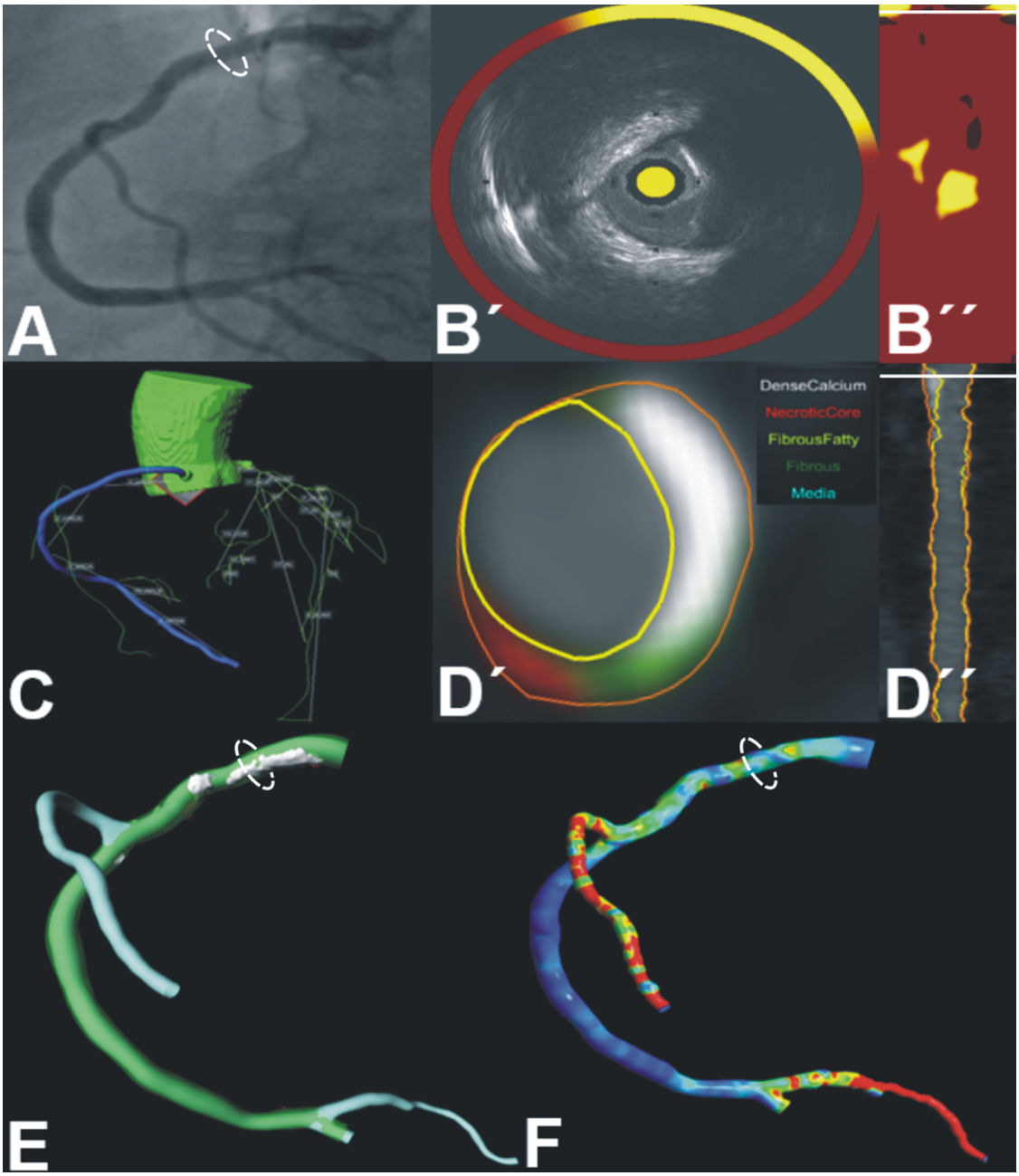

Figure 1. Example of the vessel segmentation, reconstruction and blood flow simulation for local haemodynamic forces assessment. (A). Coronary angiography of a right coronary artery (RCA). The segment of interest is defined by the most proximal and distal side branches seen on the NIRS-IVUS and CTCA. (B'). NIRS-IVUS cross-section showing an attenuated calcific plaque and (B'') the corresponding chemogram indicating the lipid-rich plaque. (C). Coronary tree model of the same patient reconstructed using CTCA where the RCA has been highlighted. (D') CTCA cross-section showing lumen (yellow) and vessel wall (orange) annotations and plaque characteristics as well as (D'') the longitudinal view of the RCA segmentation. (E). 3D reconstruction model of the RCA derived from the CTCA analysis showing luminal (light blue), vessel (green) surface and overlying plaques. (F). The ESS is a colour-coded display of the 3D model (blue colour indicates low ESS and red-high ESS).