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Research paper

Unstable coronary plaque characteristics are associated with high-sensitivity cardiac troponin T and N-terminal Pro-Brain Natriuretic Peptide

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ABSTRACT

Background: Unstable plaque characteristics on coronary CT angiography (CTA), serum high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP) concentrations are associated with cardiovascular events.
Objective: To investigate the association between coronary CTA defined quantifiable plaque characteristics, hs-cTnT and NT-proBNP.
Methods: 81 consecutive stable chest pain patients with an intermediate-to-high risk were analyzed. Coronary CTA was performed using a 64-slice multidetector-row CT-scanner. Total coronary plaque volume, calcified volume, non-calcified volume, plaque burden, remodeling index (RI) and number of plaques were measured using dedicated software. A total plaque score ("Sum plaque score") incorporating total plaque volume, RI, plaque burden and number of plaques was defined. Hs-cTnT and NT-proBNP concentrations were measured in serum samples before coronary CTA.
Results: Univariate regression analysis demonstrated significant associations of hs-cTnT and NT-proBNP with total plaque volume (r hs-cTnT = .256; r NT-proBNP = .270), calcified volume (r hs-cTnT = .344; r NT-proBNP = .344), RI (r hs-cTnT = .335; r NT-proBNP = .342) and number of plaques (r hs-cTnT = .355; r NT-proBNP = .301) (all P values $\leq$ .021). Non-calcified plaque volume showed no association with hs-cTnT and NT-proBNP (r hs-cTnT = .050; r NT-proBNP = .087; P value = .660 and P value = .442). The "Sum plaque score" showed the highest correlation compared to other plaque parameters (r hs-cTnT = .362; r NT-proBNP = .409; P value = .001 and P value $\leq$ .001).
Conclusion: Our data suggest that coronary plaque morphology parameters, derived by dedicated software, are associated with serum hs-cTnT and NT-proBNP concentrations.

1. Introduction

Despite advancements in risk score algorithms and innovative diagnostic imaging modalities, risk stratification in stable chest pain patients remains an important clinical challenge.[1] Traditional cardiovascular risk factors can identify high-risk patients, but lack ability towards personalized risk stratification. Currently, coronary CT angiography (CTA) is being widely implemented for non-invasive detection of coronary artery disease and risk

Abbreviations: ACS, Acute coronary syndrome; AMI, Acute myocardial infarction; BMI, Body mass index; CABG, Coronary artery bypass grafting; CAD, Coronary artery disease; CTA, CT angiography; cTnT, Cardiac troponin T; ECG, Electrocardiography; FRS, Framingham risk score; HDL, High density lipoprotein; Hs-cTnT, High-sensitivity cardiac troponin T; LDL, Low density lipoprotein; NT-proBNP, N-terminal Pro-Brain Natriuretic Peptide; PCI, Percutaneous coronary intervention; RI, Remodeling index.

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stratification in stable chest pain.[2–4] Classically, coronary calcium score and stenosis severity have been linked to cardiovascular events.[5–7] The presences of spotty calcification, low-attenuation plaque core and positive plaque remodeling have also been identified as risk factors for the occurrence of acute coronary syndrome (ACS).[3, 4] Recently, noninvasive quantitative coronary analysis, using dedicated software, has been proven valuable for additional risk stratification on top of conventional CT-reading in stable chest pain patients.[8]

Biomarkers have been proposed for risk stratification because of their relative ease of use.[8] Since the introduction of high-sensitivity cardiac troponin T (hs-cTnT) assays, more accurate detection of low serum troponin concentrations is possible.[9] It has previously been demonstrated that in patients with stable chest pain, levels of cardiac troponin (even those below the diagnostic cut-off value for acute myocardial infarction (AMI)), are associated with an increased risk of cardiovascular events.[10–12] It has also been described that even mild CAD (<50% luminal stenosis) is associated with quantifiable serum levels of hs-cTnT.[13] Hs-cTnT concentrations have even been correlated with a more vulnerable plaque phenotype, presuming that this could be caused by subclinical plaque rupture leading to micro-injury through dislodgement of thrombi.[14–16]

Beside hs-cTnT, N-terminal pro-B-type natriuretic peptide (NT-proBNP), as a marker for myocardial stress, has also been associated with an increased risk of death and cardiovascular events in patients with stable CAD, providing further opportunities for risk stratification.[17, 18]

Therefore, in the present study, we aimed to investigate the possible association between hs-cTnT, NT-proBNP and quantifiable coronary CTA defined high-risk plaque characteristics, using dedicated software.

2. Materials and methods

2.1. Ethics

This study is approved by the locally appointed Institutional Review Board and Ethics Committee and complies with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained in all patients.

2.2. Study population

In this study, 81 patients were included from a previously described study cohort of 126 intermediate-to-high risk stable chest pain patients who were referred for coronary CTA.[19] Patients were consecutively selected from this study cohort based upon their enrolment within the Maastricht Biomarker CT study (ClinicalTrials.gov number, NCT01671930).[19] Stable chest pain was defined as chest discomfort elicited by exertion or emotional stress and relieved by rest or nitroglycerin.

All coronary CTAs were performed between February 2008 and May 2010. All patients underwent both a coronary calcium score scan as well as coronary CTA. Exclusion criteria, as reported previously, for undergoing coronary CTA were: unstable angina pectoris, which defined as accelerated exertional angina or rest pain, hemodynamic instability, pregnancy, impaired renal function, severe iodine contrast allergy and a coronary calcium score of >1000. Additional specifications of this population have previously been published.[19]

2.3. Cardiovascular risk factors

Prior to coronary CTA, established risk factors were obtained from all patients, including arterial hypertension defined as blood pressure ≥ 140/90 mm Hg, or use of anti-hypertensive medication; active smoking; lipid profile; diabetes if diabetes mellitus was diagnosed according to the guidelines[20]; and positive family history for premature CAD which defined as having a first-degree relative with history of AMI or sudden cardiac death before the age of sixty. Additional data including height and weight were recorded. The Framingham risk score (FRS) was calculated in all individual patients.[21]

2.4. Biochemical analysis

Blood serum samples were collected prior to coronary CTA, processed within 2 hours and directly stored at −80 degrees Celsius until analysis. cTnT concentrations were measured on the Cobas 6000 analyzer (Roche Diagnostics) in a fresh aliquot. cTnT concentrations were assessed using the hs-cTnT assay of Roche Diagnostics, with diagnostic cut-off (99th percentile upper reference limit) at 14 ng/L and 10% coefficient of variation (CV) cutoff at 13 ng/L. NT-proBNP concentrations were determined using the proBNP II kit (Roche Diagnostics), reported to have a limit of detection at 0.6 pmol/L and a CV of 6.8% at 8.78 pmol/L.

2.5. Coronary CTA acquisition

Coronary CTA was performed using a 64-slice multidetector computed tomography scanner (Brilliance 64; Philips Healthcare, Best, The Netherlands) with a 64 × 0.625 mm slice collimation; rotation time of 420 ms and tube voltage of 80 or 120 kV, depending on patient's height and weight. Images were reconstructed at 0.9 mm slice thickness with an increment of 0.45 mm using XCA-D kernel (Xres standard). In addition, patients received a contrast bolus of 85–110 ml (Xenetix 350; Guerbet), which was injected in the antecubital vein at a rate of 5.0–7.2 ml/s. In patients with heart rate <65 bpm, a prospectively ECG-triggered axial acquisition was performed, in patients with heart rate >65 bpm, a retrospectively ECG-gated spiral acquisition protocol was used. Tube current varied from 150–210 mAs for the prospectively ECG-triggered axial acquisition protocol and from 600–1000 mAs for the retrospectively ECG-gated spiral acquisition protocol depending on patient's weight and height.

A non-contrast enhanced scan was performed using 120 kV and 3 mm slice thickness to determine the coronary calcium score using the Agatston method.[22] Coronary CTAs were independently analyzed by a cardiologist and a radiologist, both experienced in reading coronary CTA and blinded to clinical information using a dedicated post processing workstation for cardiac analysis (Comprehensive Cardiac, Philips Healthcare). In case of disagreement, consensus was reached by discussion. The coronary artery tree was assessed using the 16-segments American Heart Association model.[23] The degree of stenosis was visually defined and lesion severity was determined as: mild (<50%), moderate (50%-70%) and severe luminal stenosis (>70%).[24] Additionally, the "Segment involvement score" was defined by counting all coronary segments with plaques (irrespective of degree of stenosis), resulting in a score ranging from 0–16.[25]

2.6. Semi-automated plaque quantification

Quantification of volumetric and geometric plaque properties in the coronary arteries was performed using dedicated software (Comprehensive Cardiac Analysis, version 4.5.2.40007, Philips Healthcare, Fig. 1), as described previously.[19] This software reported the following parameters: maximal cross-sectional plaque area, maximal plaque burden (plaque area/vessel area*100); remodeling