Mechanisms of cardiovascular disease as defined by cardiac computed tomography

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Proefschrift

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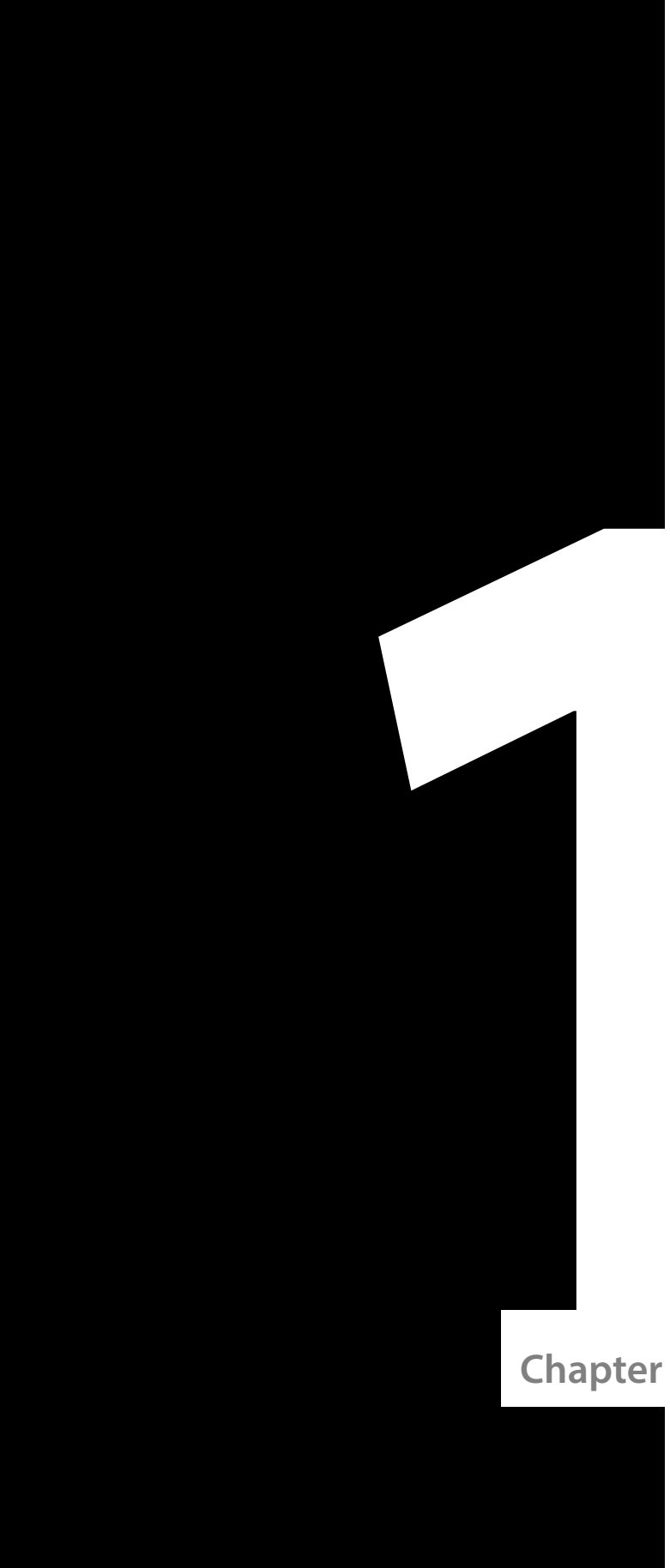

Chapter

GENERAL INTRODUCTION AND THESIS OUTLINE

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Cardiovascular disease (CVD) concerns a pre-eminent health problem worldwide. Atherosclerosis is the most prevalent underlying pathological process, which is known as a multifactorial chronic inflammatory vascular disease (1). The disruption of an atherosclerotic plaque in the epicardial arteries and subsequent intraluminal thrombus formation are the pathological hallmarks of an acute coronary syndrome, which can lead to cardiac morbidity and mortality.

Despite the advancements in understanding of the pathophysiological mechanisms of atherosclerosis and broad scale of different non-invasive and invasive imaging modalities, coronary artery disease (CAD) remains the primary source of mortality and morbidity in developed and developing countries.

Therefore, identifying patients at risk for the presence and progression of CAD and acute cardiovascular events still remains an important clinical challenge (2).

CARDIOVASCULAR RISK FACTORS AND DISEASE PREVALENCE

Currently, there are several well-established risk factors which are associated with CAD prevalence and occurrence of cardiovascular events, including male gender, increasing age, diabetes mellitus, smoking, family history of premature atherosclerosis, hypertension and dyslipidemia which are therefore widely used in different risk score algorithms.

Obesity is also recognized as a risk factor for CVD and concerns an increasing problem of the public health worldwide and is defined as a body mass index (BMI) equal or greater than 30kg/m^2 (3). The ESC guideline on the prevention of CVD lists obesity as a modifiable cardiovascular risk factor (4). Despite the clear association between obesity and cardiovascular mortality, it is a matter of debate whether obesity truly is an independent risk factor since it is strongly associated with insulin resistance, type 2 diabetes mellitus, inflammation, dyslipidaemia and hypertension, known as metabolic syndrome (5-9).

CARDIAC COMPUTED TOMOGRAPHY

Non-invasive diagnostic testing is the most important step in establishing a diagnosis in patients with suspected stable CAD (after taking the clinical pre-test probabilities for obstructive CAD into account), and can be categorized in anatomical versus functional testing.

Cardiac computed tomography (CT) is currently the preferred non-invasive imaging modality in patients with a lower range of clinical likelihood of CAD, no previous history of CAD and in patients whereby a high likelihood of good image quality can be achieved. Despite the possibility to detect subclinical coronary atherosclerosis, it is capable to accurately rule out both anatomically and functionally significant CAD and has a prominent

role in the current ESC guidelines for workup of patients with suspected CAD (10). Currently, conventional cardiac CT reading includes assessment of coronary calcium score (CCS), luminal stenosis severity and extent of CAD.

Coronary calcium score

The earliest and still used algorithm for the quantification of the coronary artery calcium (CAC) score is the so-called Agatston score and is defined as a lesion above a threshold of 130 Hounsfield units with an area of ≥3 adjacent pixels (at least 1 mm^2) (11). CAC extent measured by calcium scoring on cardiac CT is a marker of atherosclerosis and has been previously shown to be a strong and independent factor for cardiovascular events in asymptomatic patients (12-15). The Multi-Ethnic study of Atherosclerosis and Heinz Nixdorf RECALL study have shown that especially a CCS of >400 is associated with the occurrence of cardiovascular events (16). The vast majority of these early studies has demonstrated the superiority of CAC over traditional risk factors and prediction models, e.g. the Framingham Risk Score with outcome-based net reclassification improvement across different risk categories (17-19). Besides CAC extent, it is also documented that CAC progression is associated with a linear increase of coronary heart disease events (20-22).

HIGH-RISK PLAQUE MORPHOLOGY ON CARDIAC CT

Despite luminal stenosis severity, cardiac CT is also capable to visualize different unstable plaque features that have been previously identified as risk factors for the occurrence of acute coronary syndrome (ACS), namely spotty calcification, low-attenuation plaque (volume) and positive plaque remodeling (23, 24). Otsuka et al even described a specific plaque phenotype, the Napkin-ring sign which is strongly associated with future ACS events independent of other high-risk plaque features (25). The Napkin-ring sign on cardiac CT angiography (CCTA) is characterized by a plaque core with low attenuation surrounded by a rim-like area of lower attenuation (<130 Hounsfield units). According to different histopathological studies it is likely that the Napkin-ring sign is a reflection of the thin-cap fibroatheroma which is prone to rupture (26). Despite the fact that this plaque feature seems to hold on promise to identify plaques at risk, it has its limitations because of significant interobserver variability and a very low incidence of the phenomenon (4%) (25).

Additional risk stratification using cardiac CT

Novel tools for risk profiling beyond cardiac CT defined luminography are currently available, using specialized post-processing software to identify several morphologic and geometric characteristics of atherosclerotic plaques. The additional prognostic value of semi-automated plaque quantification for the development of ACS and cardiac mortality above conventional cardiac CT reading has previously been investigated and is of high interest since this approach reflects the patient at risk and could be of additional

value for risk stratification (27, 28). Defining other imaging parameters beyond coronary plaque analysis have also been put forward. There is growing evidence according to the potential impact of epicardial adipose tissue (EAT) as a separate, distinct risk factor for coronary artery disease as well as a predictor for future cardiovascular events (29-32). This has led to more insights in the pathophysiological mechanisms of EAT contributing to CVD. In regard to CAD, the close proximity of EAT to the epicardial coronary arteries directly contributes to the development and worsening of the process of atherosclerosis. EAT volume also has been linked to diastolic heart failure and atrial fibrillation based upon its close anatomic proximity as well as pro-fibrotic and pro-inflammatory effects leading to an impaired cardiac structure and function (33).

Interestingly, even calcifications of the descending aorta have been previously established as an independent predictor for future cardiovascular events which can easily be defined on CCTA (34).

BIOMARKERS

Also a promising and cost-effective way to identify patients with CAD and at risk for future cardiovascular events is the use of cardiac troponins (35, 36). Because of their unique cardiospecificity, cardiac troponins are considered the preferred biochemical markers to detect myocardial injury and to diagnose acute myocardial infarction (AMI) in particular (37). Moreover, high-sensitivity cardiac troponin concentrations turned out to have an important prognostic value for acute cardiovascular events, even below the diagnostic cut-off and beyond traditional cardiovascular risk factors (38, 39). Since the introduction of high-sensitivity cardiac troponin T (hs-cTnT) assays, more accurate detection of low serum troponin concentrations is possible (40). It has previously been demonstrated that in patients with stable CAD 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 (39, 41, 42). It has also been described that even mild CAD (<50% luminal stenosis) is associated with quantifiable serum levels of hs-cTnT (35). In addition, Hs-cTnT concentrations have 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 debris and thrombi (36, 43, 44).

Unfortunately, the shift to more sensitive assays is accompanied by a reduction in specificity, as circulating high-sensitivity cardiac troponin levels became elevated in many other conditions besides AMI (45). Renal dysfunction is one of those conditions in which elevated cardiac troponin concentrations are commonly detected (46, 47).

AIM AND OUTLINE OF THIS THESIS

This thesis aims to investigate the relationship of cardiac CT defined presence and extent of CAD and/or other detailed imaging parameters combined with serum biomarkers in

an effort to gain more insights in the diagnostic and risk stratifying capabilities of cardiac CT. Finally, we focused on the role of cardiac CT within the diagnostic work-up for suspected stable CAD in different patient populations.

Chapter 2 and ***3*** focuses on the relation between CCTA defined CAD and cardiospecific biomarkers. Moreover, in ***chapter 2*** we investigated the role of renal function and the correlation between serum hs-cTnT concentrations independent of the extent of CAD in a large cohort of patients with symptoms of chest discomfort.

In ***chapter 3*** we went a step further and investigated the association between cardiospecific biomarkers with quantifiable CCTA derived unstable plaque properties using semi-automated software in a selected study population.

Besides coronary plaque morphology, CCTA can also reveal the extent of pericardial adipose tissue using post-processing software. In ***chapter 4*** we therefore investigated the relationship between pericardial fat volume and echocardiographic parameters of diastolic function.

Chapter 5 evaluates the presence and extent of CAD in patients presenting with especially cardiac syncope at the outpatient Cardiology clinic.

In ***chapter 6*** we investigated the association of BMI with the extent of CAC in a large single-center outpatient cardiac CT cohort in order to gain new insights whether BMI alone has to be considered as an independent risk factor for CAD within an outpatient low-to-intermediate risk population.

Chapter 7 contains the general discussion and summary of the results of all above-mentioned studies and provides suggestions for future research perspectives.

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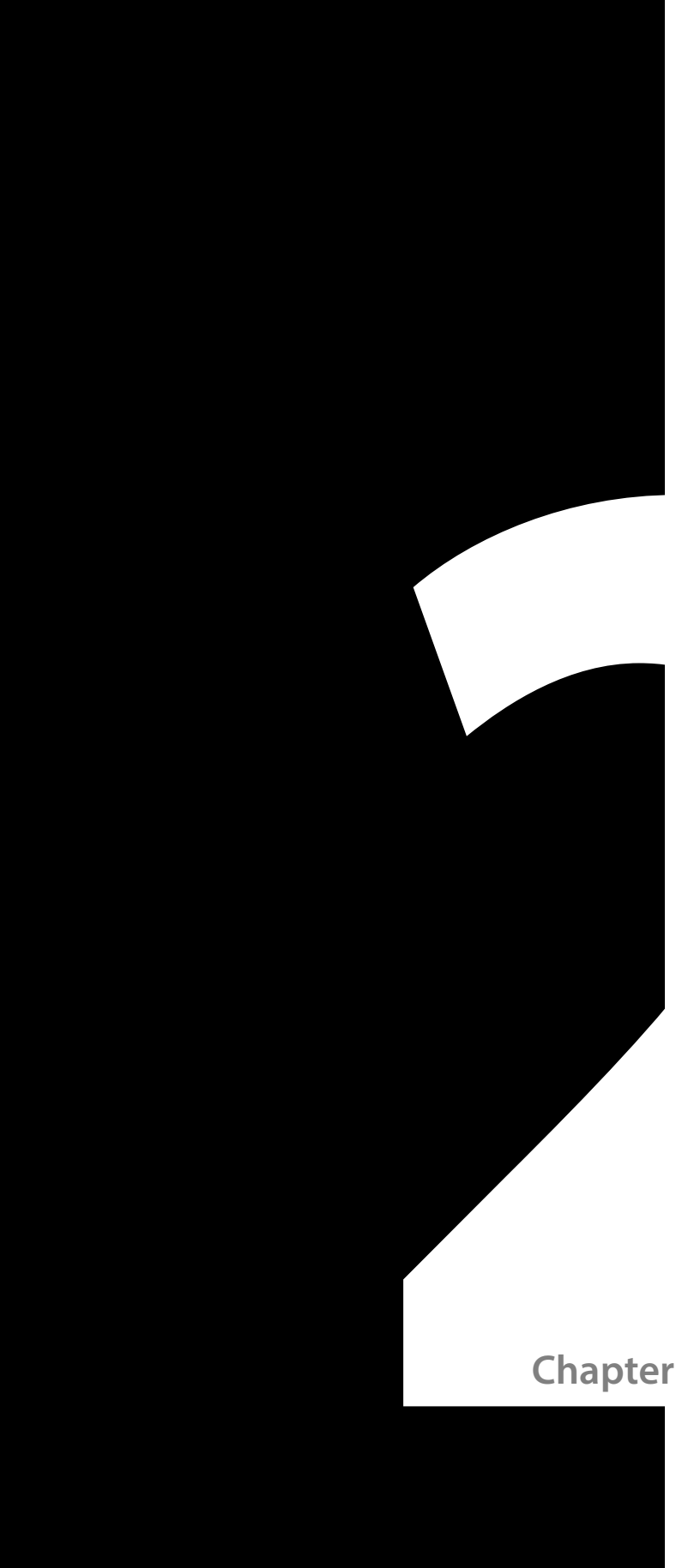

Chapter

High-sensitivity cardiac troponin concentrations in patients with chest discomfort: is it the heart or the kidneys as well?

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Abstract

BACKGROUND

High-sensitivity cardiac troponins (hs-cTn) are the preferred biomarkers to detect myocardial injury, making them promising risk-stratifying tools for patients with symptoms of chest pain. However, circulating hs-cTn are also elevated in other conditions like renal dysfunction, complicating appropriate interpretation of low-level hs-cTn concentrations.

METHODS

A cross-sectional analysis was performed in 1864 patients with symptoms of chest discomfort from the cardiology outpatient department who underwent cardiac computed tomographic angiography (CCTA). Serum samples were analyzed using hs-cTnT and hs-cTnI assays. Renal function was measured by the estimated glomerular filtration rate (eGFR), established from serum creatinine and cystatin C. On follow-up, the incidence of adverse events was assessed.

RESULTS

Median hs-cTnT and hs-cTnI concentrations were 7.2(5.8-9.2) ng/L and 2.6(1.8-4.1) ng/L, respectively. Multivariable regression analysis revealed that both assay results were more strongly associated with eGFR (hs-cTnT:stβ:-0.290;hs-cTnI:stβ:-0.222) than with cardiac imaging parameters, such as coronary calcium score, CCTA plaque severity score and left ventricular mass (all $p<0.01$). Furthermore, survival analysis indicated lower relative risks in patients with normal compared to reduced renal function for hs-cTnT [HR(95%CI), 1.02(1.00-1.03) compared to 1.07(1.05-1.09)] and hs-cTnI [1.01(1.00-1.01) compared to 1.02(1.01-1.02)] (all $p<0.001$).

CONCLUSION

In patients with chest discomfort, we identified an independent influence of renal function on hs-cTn concentrations besides CAD, that affected the association of hs-cTn concentrations with adverse events. Estimating renal function is therefore warranted when interpreting baseline hs-cTn concentrations.

INTRODUCTION

Identifying chest pain patients at risk for cardiovascular events remains an ongoing challenge (1). A promising and cost-effective way to identify those "vulnerable" patients is the use of cardiac troponins (2, 3). Because of their unique cardiospecificity, cardiac troponins T (cTnT) or I (cTnI) are considered the preferred biochemical markers to detect myocardial injury and to diagnose acute myocardial infarction (AMI) in particular (4). Since the introduction of high-sensitivity cardiac troponin (hs-cTn) assays, more accurate detection of low levels of circulating cardiac troponins became feasible (5), which significantly improved the diagnostic performance in patients with acute cardiac risk (6). Even below the diagnostic cut-off, hs-cTn concentrations turned out to have an important prognostic value for acute cardiovascular events (7-9). Moreover, in patients with stable coronary artery disease (CAD) low concentrations of hs-cTnT have been associated to the extent of CAD (2) and coronary plaque phenotypes that are more prone to rupture (3).

Unfortunately, the shift to more sensitive assays is accompanied by a reduction in specificity, as circulating hs-cTn levels are elevated in many other conditions besides AMI (7, 10). Renal dysfunction is one of those conditions in which elevated cardiac troponin concentrations are commonly detected (11, 12). Recently it was shown in chronic kidney disease (CKD) patients that elevated hs-cTn concentrations are indeed associated with reduced renal function (13). Therefore, the interpretation of baseline hs-cTn values in the individual patient is complicated not only by cardiac disease (14-16) but also renal dysfunction.

As of yet it is unknown to what extent renal function contributes to higher cardiac troponin concentrations in stable patients with chest discomfort, in whom circulating hs-cTnT concentrations are mainly attributed to the presence and severity of atherosclerotic plaques (2, 3) or echocardiographic abnormalities (17-19). In-depth understanding in which way renal function affects hs-cTnT and hs-cTnI concentrations is of utmost importance for the use of hs-cTn values in clinical practice.

This study is the first to evaluate the impact of a decreased renal function on both hs-cTnT and hs-cTnI concentrations relative to the presence of cardiovascular disease in patients who visited the cardiology outpatient department with symptoms of chest discomfort. Moreover, the renal influence on the association of hs-cTn with the incidence of adverse events is investigated.

MATERIALS AND METHODS

Study cohort

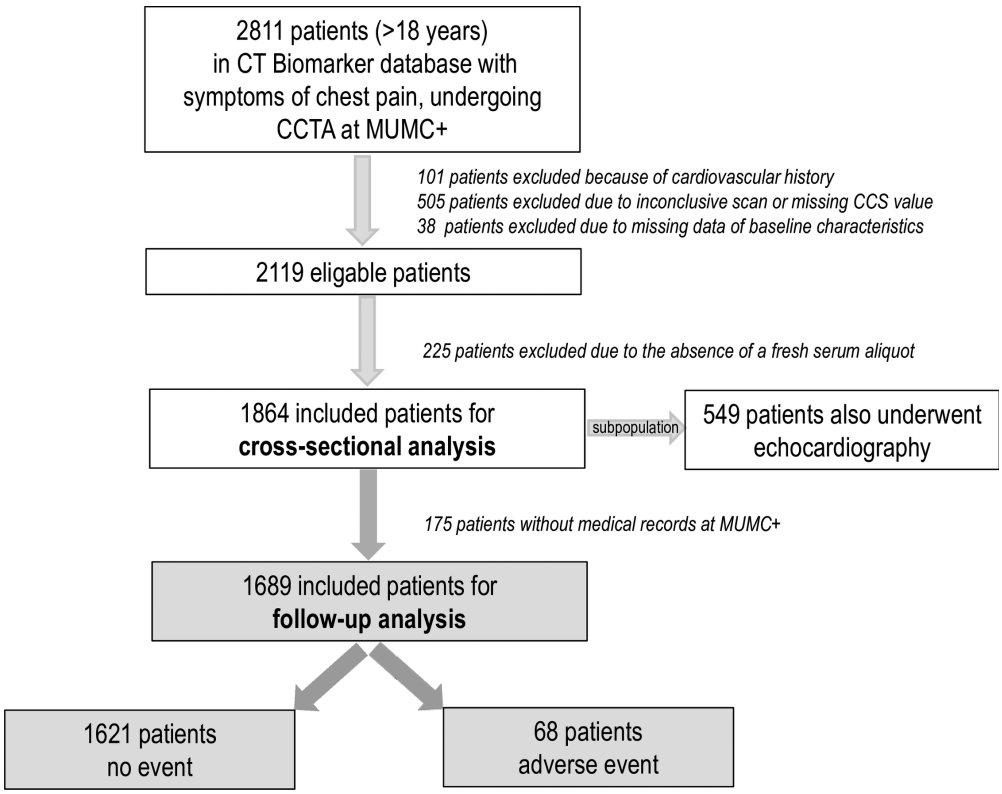
This study was approved by the Institutional Review Board (IRB) and Ethics Committee at the Maastricht University. Involved data were collected on a routine basis within the Maastricht Biomarker CT study (ClinicalTrials.gov NCT01671930, MEC 08-4-057) and data were analyzed anonymously in accordance with IRB guidelines. The study complies with the ethical principles of the Helsinki Declaration.

We analyzed a cohort of 1864 consecutive patients who were enrolled in the Maastricht Biomarker CT Study. This cohort is comprised of patients from the cardiology outpatient department presenting with (a)typical chest pain with a low-to-intermediate pretest probability who were referred for CCTA for the evaluation of stable coronary artery disease (CAD), in accordance with the current guidelines (1, 20). Included were patients of whom serum was collected prior to CCTA and excluded were patients with a previous history or diagnosis of ACS at the time of CCTA and patients with severe renal dysfunction or on dialysis (due to application of contrast fluids) (Fig. 1).

Previous results from the Maastricht Biomarker CT Study and additional specifications of this population have been published elsewhere (2, 21, 22).

FIGURE 1.

Flow chart of included and excluded patients.



Biochemical analysis

Serum samples were collected immediately before CCTA, processed within 2 hours and directly stored at -80 °C until analysis. Total cholesterol, triglycerides, high-density and

low-density lipoprotein concentrations were measured as previously described (2). Serum creatinine, cystatin C and cTnT concentrations were measured on the Cobas 6000 analyzer (Roche Diagnostics) in a fresh aliquot. Creatinine concentrations were assessed using the enzymatic method (Roche). Cystatin C was measured using a new particle-enhanced turbidimetric assay (Gentian AS), that was standardized against the certified ERM-DA471/IFCC cystatin C reference material (23). The glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equations (24) using serum creatinine and cystatin C concentrations. cTnT concentrations were determined using the high-sensitivity cTnT assay (Roche; lotnumber 167650), with a 99th percentile upper reference limit of 14 ng/L and a 10% coefficient of variation (CV) cut-off at 13 ng/L. Gender-specific cutoffs were reported at 14.5 ng/L and 10 ng/L for males and females, respectively (5). cTnI measurements were performed on the ARCHITECT i2000SR platform using the precommercial ARCHITECT STAT high-sensitivity troponin I (hs-cTnI) assay (Abbott Laboratories). According to the manufacturer, a 10% CV was reached at 4.7 ng/L and the 99th percentile cut-off concentration at 26.2 ng/L for the overall population. Gender-specific cut-offs at 34.2 ng/L and 15.6 ng/L were also defined for males and females, respectively. In duplo measurements of multiple serum samples (>20) ranging between 7-12 ng/L in hs-cTnT-concentration and 3-4 ng/L in hs-cTnI-concentration, were measured with CVs of 3% and 9% respectively.

Cardiac computed tomographic angiography

CCTAs were performed from December 2007 through December 2012 and analyzed as previously described (21). In brief, CCTA were analyzed by two experts who were blinded from hs-cTn results. The coronary calcium score (CCS) was quantified by the Agatston method (25) and luminal plaque severity as assessed by CCTA was scored as no, mild (<50% stenosis), moderate (50-70% stenosis) and severe (>70% stenosis) CAD.

Echocardiography

Echocardiography was performed in a subset of 549 patients (31%) within a period of 3 months from the CCTA scan by an expert echocardiographist, who was blinded for hs-cTn concentrations. Transthoracic images of the left ventricle (LV) were acquired to assess morphology, function and mass (Philips IE 33, Philips Medical Systems). LV function and -mass were calculated by off-line image analysis using Xcelera software package (Philips Medical Systems), according to current ESC/AHA guidelines (26). Left ventricular hypertrophy was defined as an LVmass >95 g/m^2 in females or LVmass >115 g/m^2 in males (27).

Study endpoints

Electronic patient records were monitored for the occurrence of adverse events by two reviewers. Survival time was defined as the period from date of CCTA to date of the first event or the end of follow-up (June 2013). The composite study endpoints were defined in advance as mortality and major adverse cardiovascular events, encompassing acute

coronary syndromes including AMI and unstable angina requiring hospitalization; and late coronary revascularization (>90 days after CCTA), such as percutaneous coronary interventions and coronary artery bypass grafting (22). We cannot completely rule out that CCTA outcomes presented in this study were used in the decision to perform coronary revascularization in these patients during follow up. However, we corrected for this bias by excluding the procedures that were performed within 90 days after CCTA. No records could be retrieved of 175 subjects, therefore 1689 patients (91%) of the total cohort were included for follow-up analysis.

Statistical analysis

Differences in baseline characteristics across hs-cTn categories were performed using the T-test for continuous variables with a normal distribution, Mann-Whitney U-test for non-normal distributed continuous variables and Chi square test for categorical variables. Data are presented as proportions, means ± standard deviations, and data with a non-normal distribution are given as the median (interquartile range, IQR). Pearson R correlation factors were calculated with the natural logarithm (Ln) of hs-cTnT and hs-cTnI, to normalize their skewed distribution. To assess the independent association of renal and cardiovascular parameters with hs-cTn concentrations, linear regression analyses were performed with either Ln(hs-cTnT) or Ln(hs-cTnI) as the dependent variable. Only the cardiovascular risk factors that were significantly associated to higher hs-cTnT concentrations were entered as independent variables into the multivariable model. R^2 was calculated to measure the performance of the model, and the R^2 change to address the additive effect of eGFR to the model. Interaction terms between eGFR and either CCTA and echocardiography-parameters were not statistically significant ($p>0.05$). Univariable and multivariable cox-proportional hazards models were performed to investigate the relationship of hs-cTn and the risk on adverse events during follow-up. Results are presented as hazard ratio (HR) and 95% confidence intervals (95%CI). None of the attending clinicians had access to the hs-cTnT and hs-cTnI concentrations, measured at the time of CCTA, for the diagnosis of outcome events. Statistical analysis was performed with SPSS 20.0 (SPSS). Two sided p-values of ≤0.05 were considered statistically significant.

RESULTS

Distribution and determinants of hs-cTnT and hs-cTnI

Median (IQR) hs-cTn concentrations in this cohort were 7.2 (5.8-9.2) ng/L for hs-cTnT and 2.6 (1.8-4.1) ng/L for hs-cTnI. Of all patients, 6.6% (n=123) were above the cutoff of hs-cTnT (14 ng/L) and 2.1% (n=30) above the cutoff of hs-cTnI (26.2 ng/L). Using simple linear regression, we found a strong correlation between both hs-cTn concentrations (Pearson R 0.635, $p<0.001$). However, the biological equivalent for hs-cTnI to a hs-cTnT concentration of 14 ng/L was found to be at 6.4 ng/L (S1 Fig), which is in line with recently published results (28). The majority of all patients (72%) had a normal renal function (eGFR>90 mL/min/1.73m^2) and 98% had an eGFR

above 60 mL/min/1.73m^2. The baseline characteristics are presented in Table 1 and illustrate that increasing quartiles of hs-cTnT and hs-cTnI were highly associated with traditional cardiovascular risk factors such as advancing age, male sex and increased blood pressure.

Independent association of cardiovascular disease and renal function with hs-cTn concentrations

Univariable regression analysis demonstrated that hs-cTn concentrations are significantly associated with eGFR (hs-cTnT: R:-0.396; hs-cTnI: R:-0.251; S2 Fig.), regardless of the algorithm that is used to estimate GFR (data not shown). Also, both hs-cTnT and hs-cTnI concentrations are significantly correlated with CCS (hs-cTnT: R:0.279; hs-cTnI: R:0.213) and CCTA plaque severity (hs-cTnT: R:0.307; hs-cTnI, R:0.230) (Table 2, all p<0.001).

As displayed by Figure 2, when adding renal and CT parameters as explanatory variables for hs-cTn concentrations in a multivariable regression model, both eGFR, CCS as CCTA plaque severity were identified as independent predictors (Table 2, unadjusted multivariable model).

Similar standardized β_{eGFR} ($st\beta_{eGFR}$) coefficients were observed in the univariable versus unadjusted multivariable models, indicating that CT parameters and eGFR hardly influenced each other when predicting hs-cTnT or hs-cTnI concentrations (Table 2).

After adjustment for traditional cardiovascular risk factors, eGFR, CCS and CCTA plaque severity score remained significantly associated with hs-cTn concentrations (Table 2, adjusted multivariable model 1 and 2, respectively). Also here, $st\beta_{eGFR,}$ $st\beta_{CCS}$ and $st\beta_{CCTA}$ values remain unchanged (Table 2, adjusted multivariable models 1-3).The independent contribution of eGFR to the prediction of hs-cTnT and hs-cTnI concentrations was also demonstrated by significant and identical R^2 changes (hs-cTnT: 0.056, hs-cTnI: 0.030; all p<0.001) when adding eGFR either to the baseline model or to adjusted multivariable model 2.

Furthermore, the association of eGFR with hs-cTn concentrations remained equally strong when subdividing this cohort into patients with no (hs-cTnT:$st\beta_{eGFR}$:-0.295; hs-cTnI:$st\beta_{eGFR}$:-0.228), mild (hs-cTnT:$st\beta_{eGFR}$:-0.290; hs-cTnI:$st\beta_{eGFR}$:-0.176) and moderate-to-severe CAD (hs-cTnT:$st\beta_{eGFR}$:-0.293;hs-cTnI: $st\beta_{eGFR}$:-0.249) (all p<0.001), confirming the independent influence of eGFR on hs-cTn concentrations beyond CAD severity (S1 Table). This finding was visible but less apparent for hs-cTnI than for hs-cTnT.

In a subgroup of this cohort, also echocardiographic parameters were included as explanatory variables for hs-cTn concentrations. Univariably, hs-cTnT and hs-cTnI were significantly associated with the echocardiographic measures LVEF (hs-cTnT: R:-0.151, p=0.001; hs-cTnI, R:-0.142, p=0.002) and LVmass (hs-cTnT: R:0.253; hs-cTnI: R:0.309; p<0.001) (S2 Table). In line with previous results, $st\beta_{eGFR}$ coefficients were only influenced by the confounding effects of traditional cardiovascular risk factors and not by any of the measured CT parameters or echocardiographic parameters (Table 3).

In total, 30% and 19 % of hs-cTnT and hs-cTnI variation, respectively, could be explained by the most important independent predictors: eGFR, CCS, LVmass, age and male sex (Table 3).

Table 1.

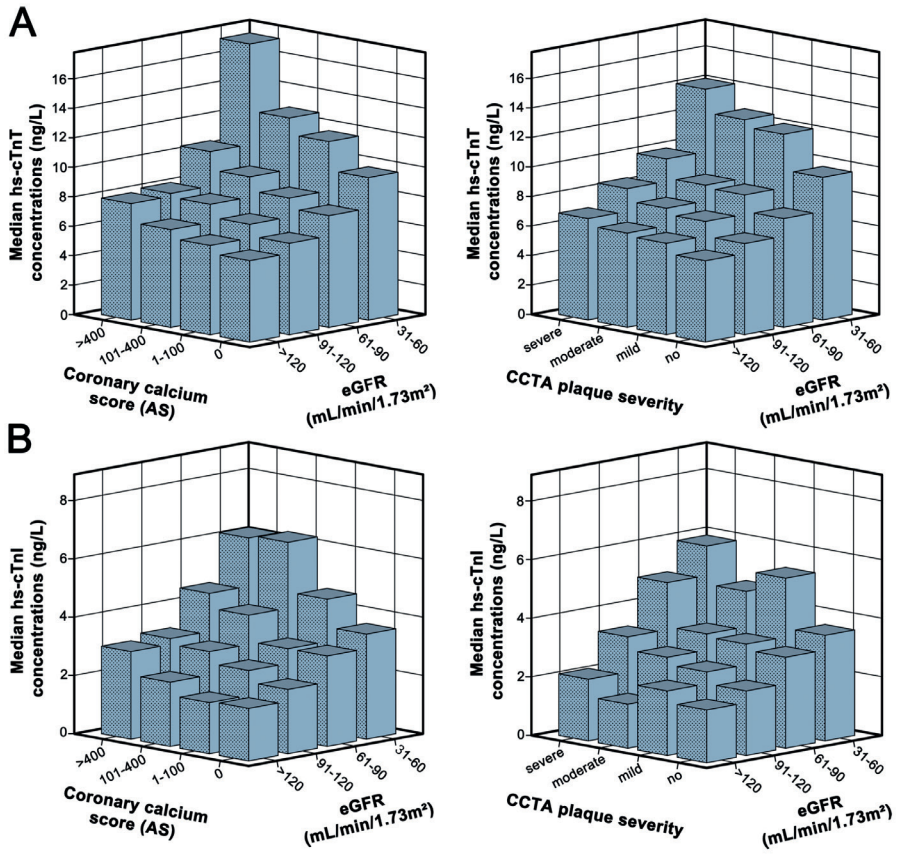
Baseline characteristics in the overall population and by median hs-cTnT and hs-cTnI concentrations.

		hs-cTnT			hs-cTnI		
Determinant	**All patients**	**≤7.2 ng/L**	**>7.2 ng/L**	**P-value**	**≤2.6 ng/L**	**>2.6 ng/L**	**P-value**
Traditional cardiovascular risk factors							
Age,years	55.8±11.0	51.8±9.9	60.4±10.2	<0.001	53.0±10.7	58.1±10.6	<0.001
Males,%	56.0	41.3	69.2	<0.001	42.7	62.6	<0.001
Body mass index,kg/m^2	27.0±4.4	26.6±4.3	27.3±4.3	<0.001	26.3±4.4	27.3±4.3	<0.001
Smokers,%	22.6	24.5	21.0	0.076	23.3	22.3	0.639
Diabetes,%	7.3	5.6	8.9	0.008	6.9	7.6	0.639
Family history,%	38.8	45.1	33.0	<0.001	43.6	36.3	0.002
Systolic blood pressure,mmHg	142.2±19.3	139.1±19.0	145.3±19.2	<0.001	138.1±18.2	144.5±19.6	<0.001
Diastolic blood pressure,mmHg	80.2±11.3	79.2±10.6	80.8±12.0	<0.001	78.3±10.8	80.9±11.6	<0.001
Total cholesterol,mmol/L	5.4±1.2	5.5±1.1	5.3±1.2	0.024	5.4±1.1	5.5±1.2	0.007
High density lipoprotein,mmol/L	1.3±0.5	1.3±0.4	1.3±0.5	0.001	1.4±0.4	1.3±0.5	0.001
Low density lipoprotein*,mmol/L	3.4±1.0	3.4±1.0	3.3±1.1	0.040	3.3±1.0	3.4±1.1	0.018
Triglycerides*,mmol/L	1.8±1.2	1.7±1.1	1.8±1.3	0.074	1.6±1.0	1.9±1.2	0.002
Estimated GFR							
CKD EPI $_{Creat\text{-}CysC}$,mL/min/1.73m^2	99.4±18.4	105.7±16.2	92.1±18.7	<0.001	105.1±17.7	95.2±18.5	<0.001
CCTA							
Coronary calcium score,AS	4.0(105.4)	0.0(0.0-25.3)	37.5(0.0-219.1)	<0.001	0.0(0.0-38.2)	16.3(0.0-167.7)	<0.001
Moderate-to-severe plaque,%	23.7	14.3	32.1	<0.001	17.4	26.7	<0.001

**indicates 250 missing values; AS, indicates Agatston score.*

FIGURE 2.

Median hs-cTnT (A) and hs-cTnI (B) concentrations according to estimated GFR categories and coronary calcium score or CCTA plaque severity. ***AS, agatston score.***



Almost identical standardized β values (stβ) for eGFR were observed when comparing adjusted multivariable models 1, 3 and 5, indicating the independent influence of eGFR on hs-cTn concentrations beyond echocardiographic parameters.

Hs-cTn remain significant and comparable prognostic markers for adverse events

Over a mean follow-up period of 2.9±1.5 years, 68 adverse events (4.0%) were observed, encompassing 33 patients who underwent late revascularization, 18 patients that suffered from a non-fatal acute coronary syndrome and 17 patients who died. From all traditional risk factors, only age, smoking and total cholesterol were significantly different in the event versus non-event group (S3 Table).

As depicted in Table 4, univariable Cox regression analysis showed that the incidence of adverse events was significantly associated with hs-cTnT and hs-cTnI. Both hs-cTn results remained highly significant predictors for adverse events when adjusted for

Table 2.

Univariable and multivariable linear regression analysis, demonstrating the independent influence of eGFR on hs-cTn concentrations beyond CCTA parameters.

	Univariable models			**Unadjusted multivariable model**		
	St β	**P-value**	**R^2**	**St β**	**P-value**	**R^2**
Dependent variable: Ln(hs-cTnT)						
eGFR	-0.396	<0.001	0.156	-0.347	<0.001	0.224
Coronary calcium score	0.279	<0.001	0.077	0.140	<0.001	
CCTA plaque severity score	0.307	<0.001	0.094	0.158	<0.001	
Age						
Female sex						
BMI						
Diabetes						
Family history						
Systolic blood pressure						
Diastolic blood pressure						
Total cholesterol						
Dependent variable: Ln(hs-cTnI)						
eGFR	-0.251	<0.001	0.063	-0.212	<0.001	0.104
Coronary calcium score	0.213	<0.001	0.045	0.113	<0.001	
CCTA plaque score	0.230	<0.001	0.052	0.122	<0.001	
Age						
Female sex						
BMI						
Diabetes						
Family history						
Systolic blood pressure						
Diastolic blood pressure						
Total cholesterol						

significant traditional risk factors and even CCS (Table 4) and CAD-severity (S4 Table). Overall, patients with elevated hs-cTnT (>14 ng/L) and hs-cTnI (>26.2 ng/L) concentrations were respectively 3 and 8 times more at risk for adverse events on follow-up.

However, renal function significantly affected the association between hs-cTnT and hs-cTnI with adverse events (p-value interaction term, <0.001 and 0.007, respectively). Higher hs-cTnT concentrations showed lower survival rates for adverse cardiac events

	Adjusted multivariable models								
	Model 1			Model 2			Model 3		
	St β	P-value	R^2	St β	P-value	R^2	St β	P-value	R^2
	-0.289	<0.001	0.323			0.282	-0.290	<0.001	0.338
				0.078	0.002		0.089	<0.001	
				0.074	0.004		0.062	0.012	
	0.254	<0.001		0.357	<0.001		0.201	<0.001	
	-0.336	<0.001		-0.278	<0.001		-0.307	<0.001	
	0.007	0.726		0.047	0.022		0.009	0.659	
	0.066	0.001		0.056	0.006		0.061	0.002	
	-0.025	0.197		-0.046	0.023		-0.033	0.085	
	0.057	0.014		0.052	0.031		0.055	0.017	
	-0.028	0.224		-0.030	0.206		-0.033	0.151	
	-0.042	0.032		-0.043	0.035		-0.036	0.069	
	-0.222	<0.001	0.145			0.129	-0.222	<0.001	0.159
				0.092	<0.001		0.101	<0.001	
				0.072	0.011		0.062	0.026	
	0.095	0.001		0.158	<0.001		0.038	0.186	
	-0.261	<0.001		-0.207	<0.001		-0.231	<0.001	
	0.031	0.174		0.061	0.006		0.032	0.145	
	-0.022	0.319		-0.032	0.152		-0.028	0.202	
	-0.013	0.544		-0.032	0.158		-0.022	0.317	
	0.098	<0.001		0.094	<0.001		0.096	<0.001	
	-0.017	0.522		-0.019	0.467		-0.022	0.400	
	0.018	0.435		0.018	0.431		0.025	0.266	

when eGFR was <90 mL/min/1.73m^2 in comparison when eGFR was ≥90 mL/min/1.73m^2 (as illustrated by the Kaplan-Meier curves in S3 Fig). Consequently, in patients with eGFR <90mL/min/1.73m^2, a 1 ng/L-rise in hs-cTnT and hs-cTnI resulted in an increased relative risk of 7.1% and 1.5% respectively. However this increase in relative risk was 4 to 2 times less for hs-cTnT (2%) and hs-cTnI (0.6%) in patients with normal renal function (eGFR ≥90 mL/min/1.73m^2).

Table 3.

Adjusted multivariable linear regression analysis for the influence of CT and echocardiographic parameters and eGFR on hs-cTn concentrations (N=549/1864). Almost identical standardized β values (stβ) for eGFR were observed when comparing adjusted multivariable models 1, 3 and 5, indicating the independent influence of eGFR on hs-cTn concentrations beyond echocardiographic parameters.

	Adjusted multivariable models														
	Model 1			**Model 2**			**Model 3**			**Model 4**			**Model 5**		
	St β	**P-value**	**R^2**	**St β**	**P-value**	**R^2**	**St β**	**P-value**	**R^2**	**St β**	**P-value**	**R^2**	**St β**	**P-value**	**R^2**
Dependent variable: LN(hs-cTnT)															
eGFR	-0.244	<0.001	0.261			0.241	-0.247	<0.001	0.282			0.256	-0.254	<0.001	0.298
LVmass				0.132	0.004		0.136	0.003		0.139	0.002		0.144	0.001	
LVEF				-0.074	0.077		-0.075	0.065		-0.065	0.115		-0.066	0.101	
Coronary calcium score										0.132	0.002		0.142	0.001	
Age	0.255	<0.001		0.378	<0.001		0.245	<0.001		0.335	<0.001		0.195	<0.001	
Gender	-0.288	<0.001		-0.212	<0.001		-0.228	<0.001		-0.193	<0.001		-0.208	<0.001	
BMI	-0.016	0.700		-0.018	0.676		-0.048	0.247		-0.017	0.687		-0.048	0.242	
Diabetes	0.076	0.064		0.062	0.135		0.067	0.099		0.064	0.118		0.069	0.083	
Family history	-0.040	0.312		-0.037	0.357		-0.025	0.534		-0.037	0.359		-0.024	0.543	
Systolic BP	0.041	0.396		0.026	0.593		0.022	0.639		0.029	0.542		0.026	0.582	
Diastolic BP	-0.060	0.200		-0.046	0.337		-0.051	0.271		-0.055	0.240		-0.062	0.179	
Total cholesterol	-0.079	0.053		-0.072	0.081		-0.069	0.086		-0.066	0.109		-0.062	0.118	
Dependent variable: LN(hs-cTnI)															
eGFR	-0.207	<0.001	0.120			0.141	-0.213	<0.001	0.171			0.160	-0.220	<0.001	0.191
LVmass				0.225	<0.001		0.229	<0.001		0.234	<0.001		0.238	<0.001	

Table 3. *(continued)*

	Adjusted multivariable models													
	Model 1			Model 2			Model 3			Model 4			Model 5		
	St β	P-value	R^2	St β	P-value	R^2	St β	P-value	R^2	St β	P-value	R^2	St β	P-value	R^2
LVEF				-0.080	0.071		-0.081	0.063		-0.070	0.109		-0.071	0.100	
Coronary calcium score										0.150	0.001		0.157	<0.001	
Age	0.085	0.008		0.185	<0.001		0.068	0.199		0.136	0.005		0.014	0.804	
Gender	-0.253	<0.001		-0.141	0.003		-0.155	0.001		-0.120	0.012		-0.134	0.005	
BMI	0.010	0.821		-0.020	0.654		-0.046	0.308		-0.019	0.669		-0.045	0.307	
Diabetes	-0.019	0.674		-0.032	0.465		-0.028	0.517		-0.030	0.496		-0.025	0.555	
Family history	-0.019	0.656		-0.009	0.834		0.001	0.978		-0.009	0.838		0.002	0.965	
Systolic BP	0.110	0.037		0.081	0.123		0.080	0.121		0.084	0.105		0.083	0.102	
Diastolic BP	-0.071	0.171		-0.047	0.356		-0.055	0.276		-0.058	0.252		-0.066	0.183	
Total cholesterol	-0.031	0.489		-0.020	0.649		-0.017	0.691		-0.013	0.765		-0.010	0.820	

Table 4.

Cox proportional regression analysis for the association of hs-cTnT and hs-cTnI with adverse events in all patients or when stratified for eGFR ≥or <90mL/min/1.73m².

	All patients ***(n=1689, 68 events)***				**eGFR≥90mL/min/1.73m²** ***(n=1192, 34 events)***				**eGFR<90mL/min/1.73m²** ***(n=497, 34 events)***			
	univariable		**Multivariable***		**univariable**		**Multivariable***		**univariable**		**Multivariable***	
	HR (95%CI)	**P-value**	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**
Hs-cTnT (ng/L)	1.025 *(1.016-1.033)*	<0.001	1.028 *(1.017-1.039)*	<0.001	1.018 *(1.003-1.034)*	0.020	1.019 *(1.002-1.037)*	0.031	1.071 *(1.048-1.094)*	<0.001	1.076 *(1.043-1.111)*	<0.001
Hs-cTnT >99th perc **(=14 ng/L)**	4.806 *(2.698-8.561)*	<0.001	2.804 *(1.495-5.260)*	0.001	3.289 *(1.158-9.342)*	0.025	2.321 *(0.770-7.00)*	0.135	4.631 *(2.217-9.673)*	<0.001	2.909 *(1.287-6.572)*	0.010
Hs-cTnI **(ng/L)**	1.007 *(1.004-1.010)*	<0.001	1.008 *(1.005-1.012)*	<0.001	1.006 *(1.002-1.010)*	0.002	1.007 *(1.003-1.011)*	0.001	1.015 *(1.007-1.022)*	<0.001	1.014 *(1.005-1.024)*	0.001
Hs-cTnI >99th perc (26.2 ng/L)	10.250 *(5.218-20.13)*	<0.001	7.768 *(3.814-15.82)*	<0.001	9.529 *(3.685-24.64)*	<0.001	8.239 *(3.012-22.54)*	<0.001	10.875 *(4.162-28.42)*	<0.001	11.147 *(3.868-32.12)*	<0.001

**multivariable models are also adjusted to age, gender, smoking, total cholesterol and CCS.*

DISCUSSION

The present study provides new insights into the interpretation of hs-cTn concentrations in patients with chest discomfort, identifying not only cardiac parameters but also renal function as independent and strong contributors to circulating hs-cTn concentrations. In fact, eGFR exhibited limited confounding effects on the association between hs-cTn and stable CAD but did interfere with the association between hs-cTn and the risk on adverse events, such as mortality and AMI.

Influence of renal function on hs-cTnT and hs-cTnI concentrations

In patients with chest discomfort, we found that hs-cTnT and hs-cTnI were strongly correlated with eGFR. Also in patients with noncardiac cause of chest pain, eGFR was found to be next to age an important determinant for hs-cTnT concentrations (29). Even within normal eGFR boundaries, our results clearly demonstrate that a decreased renal clearance is associated with hs-cTn concentrations. Although differences were small, hs-cTnT was more strongly correlated with eGFR than hs-cTnI, which was also reported in subjects with moderate-to-severe CKD (13, 30). In addition, the association between hs-cTnT concentrations and eGFR were stronger than any known associations between hs-cTnT and cardiac parameters, such as coronary plaque severity (2, 3, 31) or left ventricular structure (16, 18, 32). Interestingly, this is in contrast to hs-cTnI, in which the association with LVmass was greater than with eGFR. For clinical decision making, hs-cTnT and hs-cTnI assays are currently used interchangeably from each other. However, these findings suggest that hs-cTnT could be more susceptible to changes in renal clearance than hs-cTnI. Future research should further examine these differences between hs-cTnT and hs-cTnI.

Renal and cardiac parameters are two independent contributors to hs-cTn

Importantly, we demonstrate for the first time that the extent of stable CAD and echo-cardiographic characteristics of the left ventricle did not interfere with the magnitude of the association between eGFR and hs-cTn concentrations. As a consequence, in non-acute patients with a normal to mildly impaired kidney function, decreases in renal function and the extent of stable CAD can be considered as two contributors of hs-cTn accumulation. Further research is necessary to examine the association of hs-cTn with renal function relative to cardiovascular disease in populations such as acute chest pain and chronic heart failure patients.

The significant association between eGFR and hs-cTn concentrations, independent from cardiac pathologies, is in line with the observation that cTnT and cTnI are cleared by the kidneys (33, 34). However, we cannot exclude that a decreased renal function may exert additional myocardial stress that is not identified by cardiac imaging, leading to subsequent cardiac troponin release. We were able to explain up to 30% of the variation in hs-cTn concentrations, and therefore unknown or undetected pathologies to the myocardium can also result in cTn release that was not taken into account.

Furthermore, these findings provide an explanation for the reduced diagnostic performance of hs-cTn seen in AMI patients with lower renal function in comparison to those with normal renal function (35, 36). Therefore, when acquiring the diagnostic hs-cTn cutoffs from reference populations (99th upper reference limit), it is of equal importance to screen for renal as for cardiac health.

Significant influence of renal function on the prognostic value of hs-cTn

In this study, we found that serum hs-cTnT as well as hs-cTnI were significant prognostic markers for the prediction of adverse events, independent from other established risk predictors, such as CCS. These results therefore indicate that both hs-cTn are not only useful risk stratifyers in patients

When adjusted for decreased renal function, hs-cTnT and hs-cTnI remain significant prognostic markers for adverse events, as found in other study populations (38, 39), although renal function significantly modified this association. Therefore, increases in hs-cTnT and hs-cTnI indicate respectively 4 and 2 times more risk in patients with reduced renal function compared to patients with normal renal function. The rationale behind these results could be in line with previous findings that patients with decreased renal function are more at risk for developing events (40, 41). Moreover, the attenuation in hazard ratios was more pronounced for hs-cTnT than hs-cTnI, and correspond to our previous observation that hs-cTnT was more associated with renal function than hs-cTnI. Nonetheless, in the patients with both reduced and normal eGFR, hs-cTnT and hs-cTnI concentrations hold an important prognostic value besides important risk predictors such as CCS, age and smoking. Prospective studies must establish whether baseline hs-cTn concentrations should therefore be accompanied by GFR-assessment.

CONCLUSION

In conclusion, we identified in patients with symptoms of chest discomfort that renal function has a moderate and independent influence on circulating hs-cTnT and hs-cTnI concentrations. Moreover, renal function significantly affected the association of hs-cTnT and hs-cTnI with adverse events. Therefore, our results seriously question whether baseline hs-cTn concentrations should be reported without the access to an eGFR.

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Supplementary
FILES

FIGURE S1.

Scatterplots and simple linear regression of the association between Ln(hs-cTnT) and Ln(hs-cTnI). The regression line follows the linear function y= 1.37 x - 1.75.

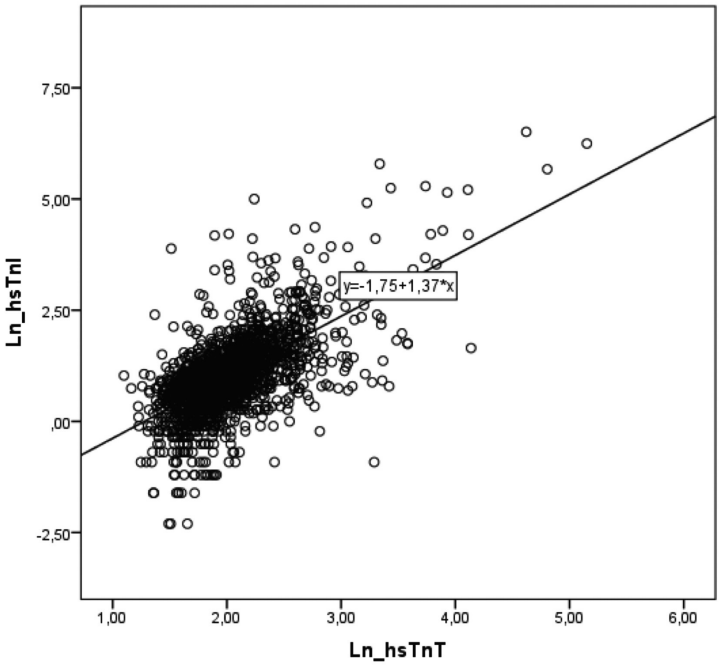

Table S1.

Association of hs-cTnT or hs-cTnI concentrations with (A) eGFR in patients without CAD (n= 756), mild (n= 667) and moderate-to-severe CAD (n= 441) and (B) CCS in patients with *eGFR < 90 mL/min/1.73m² (n=524) and eGFR >= 90 mL/min/1.73m² (n=1340)* , indicating almost identical unstandardized and standardized β values for eGFR ($st\beta_{eGFR}$) and CCS ($st\beta_{CCS}$) across these different categories. *, indicates Stβ obtained from the regression model containing also the variables age, gender, BMI, Family history, Systolic BP, diastolic BP and totalcholesterol; †, p<0.001.

		Dependent variable: Ln(hs-cTnT)		Dependent variable: Ln(hs-cTnI)	
A. CCTA plaque severity		**St β_{eGFR}(95%CI)***	**R^2**	**St β_{eGFR}(95%CI)***	**R^2**
No CAD	eGFR	-0.295 (-0.373;-0.218)†	0.237	-0.228 (-0.313;-0.144)†	0.107
Mild CAD	eGFR	-0.290 (-0.368;-0.213)†	0.297	-0.176 (-0.264;-0.088)†	0.094
Moderate-to-severe CAD	eGFR	-0.293 (-0.386;-0.200)†	0.275	-0.249 (-0.350;-0.148)†	0.151
B. eGFR category		**St β_{eGFR}(95%CI)***	**R^2**	**St β_{eGFR}(95%CI)***	**R^2**
eGFR < 90 mL/ min/1.73m²	CCS	0.121 (0.043-0.199)	0.287	0.119 (0.032-0.206)	0.121
eGFR >= 90 mL/ min/1.73m²	CCS	0.123 (0.072-0.174	0.226	0.140 (0.085-0.195)	0.109

FIGURE S2.

Scatterplots of the association of eGFR with Ln (hs-cTnT) (A) and Ln (hs-cTnI) (B).

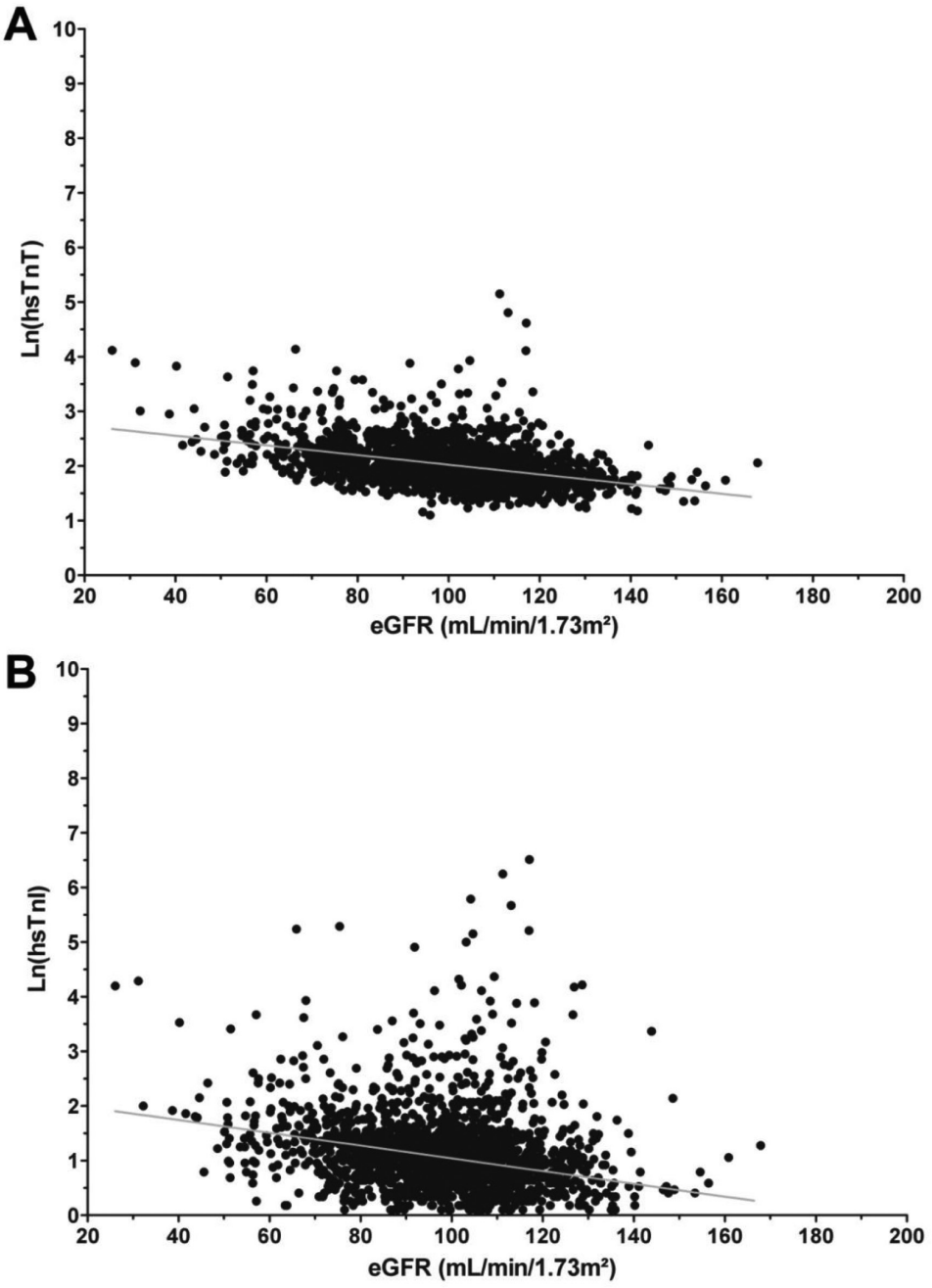

Table S2.

Baseline characteristics of subpopulation (N=549/1876 patients) **in which echocardiography was performed,** by median hs-cTnT and hs-cTnI concentrations.

		hs-cTnT			hs-cTnI		
Determinant	**All patients**	**≤7.2 ng/L *(N=231)***	**>7.2 ng/L *(N=318)***	**P-value**	**≤2.6 ng/L *(N=163)***	**>2.6 ng/L *(N=386)***	**P-value**
Echocardiography							
Left ventricular ejection fraction,%	60.0±7.3	60.7±5.9	59.4±8.2	0.037	60.8±5.5	59.6±8.0	0.056
Left ventricular mass, g	169.3±45.0	158.0±37.0	178.0±48.6	<0.001	155.0±33.6	175.9±48.0	<0.001
Left ventricular mass index, g/m^2	87.4±20.0	83.2±16.6	90.7±21.8	<0.001	82.5±16.1	89.7±21.2	<0.001

Table S3.

Differences in baseline characteristics between the event and event-free group.

Determinant	**Event *(N=68)***	**No event *(N=1621)***	**P-value**
Traditional risk factors			
Males	44 (64.7%)	899 (55.5%)	0.137
Age, years	61.4 ± 11.7	56.1 ± 10.7	<0.001
BMI, kg/m^2	27.0 ± 5.0	27.0 ± 4.3	0.913
Smokers	39.7%	21.7%	0.001
Diabetes	7 (10.3%)	121 (7.5%)	0.351
Fam. history	23 (33.8%)	621 (38.3%)	0.525
Systolic BP, mmHg	143.8 ± 17.8	142.6 ± 19.5	0.591
Diastolic BP, mmHg	78.7 ± 13.0	80.1 ± 11.4	0.287
Total cholesterol, mmol/L	5.1 ± 1.4	5.4 ± 1.2	0.040
Cardiac biochemical markers			
hs-cTnT, ng/L	9.0 (7.0-13.8)	7.2 (5.8-9.1)	0.002
hs-cTnI, ng/L	3.7 (2.4-10.1)	2.7 (1.8-4.1)	0.021
Renal clearance			
Cystatin C, mg/L	0.89 ± 0.29	0.77 ± 0.17	0.001
Creatinine, µmol/L	80.8 ± 22.2	74.8 ± 15.6	0.031
$eGFR_{creat+cysC}$, mL/min/1.73m^2	89.3 ± 22.1	99.2 ± 18.1	<0.001
CT/CCTA parameters			
Coronary calcium score, AS	175.4 (8.3-556.7)	4.3 (0-102)	<0.001
Moderate-to-severe plaque	44 (64.7%)	371 (22.9%)	<0.001
Data is indicated as either: n (%), mean (±SD) or median (IQR)			

FIGURE S3.

Kaplan-Meier curves for the estimation of risk on all-cause mortality according to different eGFR and hs-cTnT or hs-cTnI categories. hs-cTnThigh indicates hs-cTnT > 4th quartile (= 9.2 ng/L); hs-cTnTlow, hs-cTnT <4th quartile; hs-cTnIhigh, hs-cTnI >4th quartile (4.1 ng/L); hs-cTnIlow, hs-cTnI <4th quartile; eGFRnormal indicates eGFR >90 mL/min/1.73m^2; eGFRreduced eGFR, <90 mL/min/1.73 m^2.

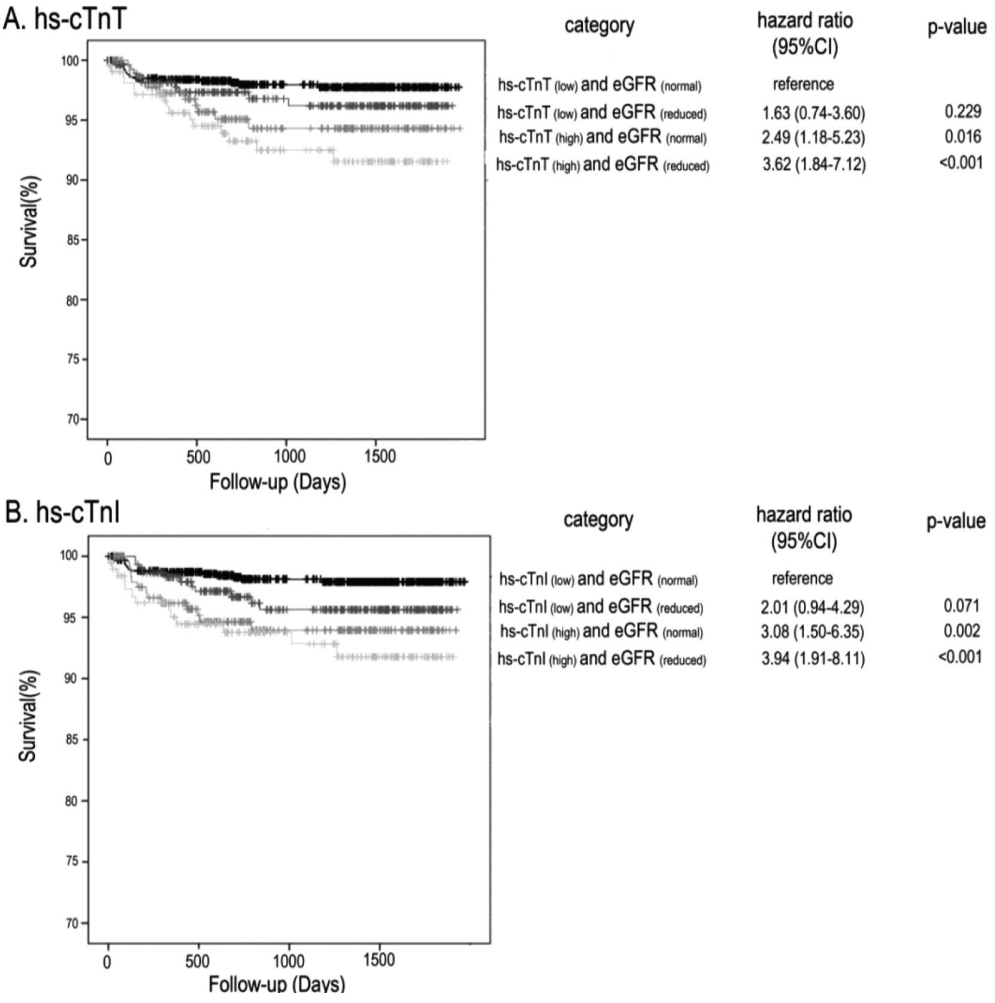

Table S4.

Cox proportional regression analysis for the association of hs-cTnT and hs-cTnI with adverse events in all patients or when stratified for eGFR ≥or <90mL/min/1.73m^2. All models were adjusted to age, gender, smoking, total cholesterol and CAD-severity score.

	All patients ***(n=1689, 68 events)***		**eGFR≥90mL/min/1.73m^2** ***(n=1192, 34 events)***		**eGFR<90mL/min/1.73m^2** ***(n=497, 34 events)***	
	HR (95%CI)	**P-value**	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**
Hs-cTnT	1.060 *(1.034-1.086)*	<0.001	1.020 *(1.003-1.037)*	0.021	1.071 *(1.040-1.104)*	<0.001
Hs-cTnT >99th perc	3.133 *(1.666-5.890)*	<0.001	2.886 *(0.996-8.361)*	0.051	2.959 *(1.307-6.698)*	0.009
Hs-cTnI	1.008 *(1.005-1.012)*	<0.001	1.007 *(1.003-1.011)*	0.001	1.012 *(1.003-1.021)*	0.007
Hs-cTnI >99th perc	8.528 *(4.259-17.08)*	<0.001	9.459 *(3.614-24.757)*	<0.001	8.734 *(3.114-24.49)*	<0.001

Chapter

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 ≤ .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 ≤ .001).

CONCLUSION

Our data suggest that coronary plaque morphology parameters, derived by dedicated software, are associated with serum hs-cTnT and NT-proBNP concentrations.

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 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.

MATERIALS AND METHODS

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.

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).

Cardiovascular Risk Factors

Prior to coronary CTA, established risk factors were obtained from all patients, including arterial hypertension defined as blood pressure ≥ 140/90mm 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).

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 14ng/L and 10% coefficient of variation (CV) cutoff at 13ng/L. NT-proBNP concentrations were determined using the proBNP II kit (Roche Diagnostics), reported to have a limit of detection at 0.6pmol/L and a CV of 6.8% at 8.78pmol/L.

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 x 0.625 mm slice collimation; rotation time of 420ms 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).

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, figure 1), as described previously (19).

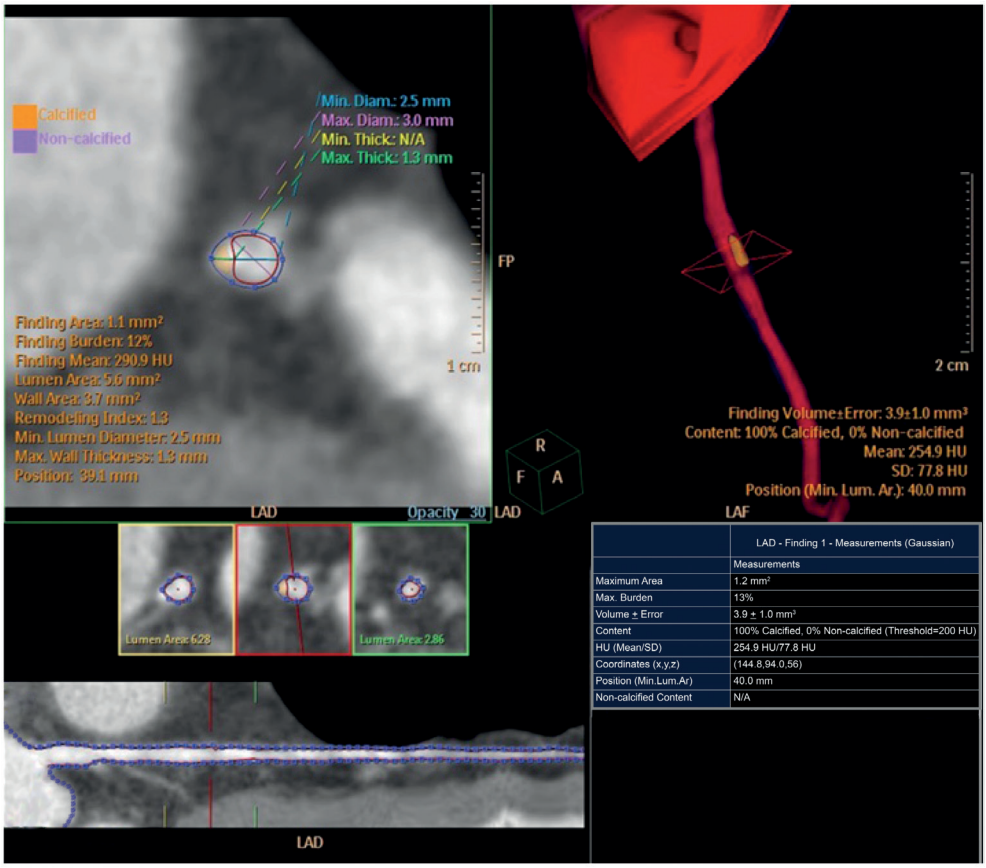
This software reported the following parameters: maximal cross-sectional plaque area, maximal plaque burden (plaque area/vessel area*100); remodeling index (RI), as well as volumetric measurements of the plaque: calcified volume, non-calcified volume. In addition to per plaque parameters that were reported by the software, total plaque parameters were calculated to enable a per patient analysis. Finally, the "Sum plaque score" was calculated in all patients, as the sample size of the study limited the ability to perform multivariate regression analysis; incorporating total plaque volume, RI, plaque burden and number of plaques. This score was calculated according to the median of these constituent parameters within the total study population. One point was given if the concerning parameter, at patient level, was equal or higher than the median value of the total study population. The sum of this led to a total score ranging from 0-4.

Follow-up and outcome

Electronic patient records were monitored for outcome, namely ACS, including myocardial infarction and unstable angina, occurrence of unplanned revascularization procedures (percutaneous coronary intervention or coronary artery bypass grafting (CABG)) and cardiac mortality. ACS was defined as typical angina pectoris and troponin T elevation (>0.01µg/L) and ST-segment elevation/depression of equal or larger than 1 mm, or at least two of these symptoms together with invasive angiographic confirmation of a culprit lesion (26). An independent cardiologist blinded for coronary CTA, hs-cTnT and NT-proBNP concentrations reviewed all events.

FIGURE 1.

Example of plaque analysis using dedicated software. In this example the mid segment of the left anterior descending artery showed a calcified plaque.



Statistical analysis

Data were analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Normality of data distribution was evaluated using the Kolmogorov-Smirnov test. Continuous data were reported as means and standard deviations (SD) if normally distributed. Not normally distributed continuous variables were reported as median and interquartile range (IQR). Differences were assessed using the independent sample T-test or the Mann-Whitney U test. Proportions (%) were used for categorical values. Differences for proportions were measured using the Chi-square test. Hs-cTnT, NT-proBNP and the total plaque parameters were normalized by logarithm transformation. To investigate the associations between the cardiospecific biomarkers and the plaque parameters, correlations were calculated according to the Pearson's correlation coefficient within a univariate linear regression model with hs-cTnT and

NT-proBNP as dependent variables. Confidence intervals (95%) for the Pearsons's correlation coefficient were calculated. All *P* values were 2-sided, and a *P* value of < .05 was considered statistically significant.

RESULTS

Study population

Table 1 lists the baseline characteristics of the study population. Mean age (± SD) of the total population was 60 ±10 years and 52 (64%) were male. Median coronary calcium score was 62 [Interquartile range (IQR) 9 to 259]. The prevalence of mild, moderate and severe luminal diameter stenosis was 35%, 36% and 29%, respectively. The median FRS was 25% in the overall study population. Median hs-cTnT concentrations were 8.3 [IQR 7 to 10.4] ng/L and median NT-proBNP concentrations were 10.1 [IQR 3.9 to 19.9] pmol/L. Age, body mass index (BMI) and the FRS were both significantly higher within the hs-cTnT as well as NT-proBNP above the median group (all *P* values < .05).

Association of hs-cTnT and NT-proBNP with conventional coronary CTA parameters

The coronary calcium score differed significantly between the NT-proBNP groups (median 35 versus 139; *P* value = .034) but not between the hs-cTnT groups (median 31 versus 85; *P* value = .362). Luminal stenosis severity was not statistically different between in both hs-cTnT and NT-proBNP categories (*P* value = .246 and *P* value = .204). In contrast to luminal stenosis, the "Segment involvement score" significantly differed across both hs-cTnT and NT-proBNP categories (median 2 versus 4; *P* values ≤.005) (Table 1). The "Segment involvement score" was significantly associated with hs-cTnT and NT-proBNP (*r* hs-cTnT = .320; *r* NT-proBNP = .355; *P* value= .004 and *P* value= .001; Table 2).

Association of hs-cTnT and NT-proBNP with plaque quantification parameters

Patients within hs-cTnT above the median had a significantly higher RI (median 4.1 versus 2.3), number of plaques (median 3 versus 2) and "Sum plaque score" (median 1 versus 3) compared to patients with hs-cTnT under the median (all *P* values ≤ .023).

Patients with NT-proBNP above the median also had a significantly higher RI and "Sum plaque score" compared to patients with NT-proBNP under the median (median 4.1 versus 2.5; median 3 versus 1; *P* value = .033 and *P* value = .043). Other plaque parameters showed a trend towards higher plaque burden in patients with hs-cTnT and NT-proBNP above median. However, this did not reach statistical significance (Table 1).

Univariate linear regression analysis (Table 2) with log-transformed data demonstrated that hs-cTnT and NT-proBNP serum concentrations were significantly associated with total plaque volume (*r* hs-cTnT = .256; *r* NT-proBNP =. 270), total calcified volume (*r* hs-cTnT = .344; *r* NT-proBNP = .344), total RI (*r* hs-cTnT = .335; *r* NT-proBNP = .342) and total number of plaques (*r* hs-cTnT= .355; *r* NT-proBNP= .301) (all *P* values ≤ .021). Non-calcified volume showed no association with hs-cTnT and

Table 1.

Baseline characteristics of the study population according to hs-cTnT and NT-proBNP median.

	Total *n=81*	**hs-cTnT ≤ 8.3ng/L** *n=41*	**hs-cTnT > 8.3ng/L** *n=40*	***P* value**	**NT-proBNP ≤ 10.1pmol/L** *n=41*	**NT-proBNP > 10.1pmol/L** *n=40*	***P* value**
Age	60 ± 10	57 ± 8	62 ± 10	.007	56 ± 9	63 ± 9	.001
Male gender, %	52 (64)	20 (49)	32 (80)	.003	32 (78)	20 (50)	.479
BMI, kg/m^2	28±5	27 ± 5	29 ± 4	.043	29 ± 4	27 ±5	.049
Active smoking, %	17 (21)	11 (27)	6 (15)	.191	8 (19)	9 (22)	.741
Diabetes mellitus, %	8 (10)	2 (5)	6 (15)	.127	5 (12)	3 (7)	.479
Positive family history, %	38 (47)	24 (59)	14 (35)	.034	21 (51)	17 (41)	.432
Systolic BP, mmHg	149 ± 21	146 ± 23	152 ± 20	.205	144 ±20	155 ±22	.017
Diastolic BP, mmHg	83 ± 12	80 ± 11	85 ±12	.054	82 ± 12	86 ±13	.292
Cholesterol, mmol/L	5.5 ±1.4	5.7 ± 1.3	5.4 ± 1.5	.327	5.7 ±1.3	1.3 ±0.4	.383
HDL cholesterol, mmol/L	1.3 (1-1.5)	1.3 (1-1.7)	1.1 (0.9-1.5)	.042	1.2 (1-1.5)	1.3 (1-1.6)	.703
LDL cholesterol, mmol/L	3.1 (2.2-4.7)	3.4 (2.4-4.7)	2.8 (2-4.6)	.353	3.7 (2.4-4.8)	2.8 (2-4.4)	.260
Triglycerides, mmol/L	1.6 (1-2.4)	1.6 (0.9-2.3)	1.8 (1.3-2.6)	.179	1.5 (1-2.4)	1.7 (1-2.6)	.367
hs-cTnT, ng/L	8.3 (7-10.4)	--	--		7.7 (6.5-9.2)	8.9 (7.4-11.3)	.035
NT-proBNP, pmol/L	10.1 (3.9-19.9)	8.3 (3.1-17.4)	12.8 (4.8-21.2)	.154	--	--	--
Creatinine, µmol/L	78 ± 19	72 ± 14	84 ±22	.005	80 ± 17	76 ±21	.412
eGFR, mL/min/1.73m^2	86 ± 21	93 ± 21	79 ± 19	.002	91 ±20	81 ±22	.046
Framingham risk score	25 (12-37)	16 (9-27)	30 (18-44)	.001	18 (11-28)	31 (16-44)	.012
Calcium score, AU*	62 (9-259)	31 (8-190)	85 (14-280)	.362	35 (4-161)	139 (14-280)	.034

Table 1. *(continued)*

	Total *n= 81*	**hs-cTnT ≤ 8.3ng/L** *n=41*	**hs-cTnT > 8.3ng/L** *n=40*	***P* value**	**NT-proBNP ≤ 10.1pmol/L** *n=41*	**NT-proBNP > 10.1pmol/L** *n=40*	***P* value**
CCTA luminal stenosis, %				.246			.204
Mild, <50%	28 (35)	17 (41)	11 (27)		14 (34)	14 (35)	
Moderate, 50-70%	29 (36)	15 (37)	14 (35)		18 (44)	11 (27)	
Severe, >70%	24 (29)	9 (22)	15 (38)		9 (22)	15 (38)	
Plaque volume, mm³	51 (11-113)	27.9 (7-102)	58.4 (23.9-120)	.219	27.9 (11.2-64)	80.4 (13.7-121.4)	.116
Calcified volume, mm³	32 (7-82)	11.8 (4.9-89)	48 (17-74)	.096	16 (6.2-51.2)	53 (9.7-90.3)	.065
Non-calcified volume, mm³	7 (0-30)	4.2 (0-25.6)	8.5 (1-35)	.319	7.3 (0-30)	6.7 (1.5-31.5)	.333
Burden, %	70 (30-142)	48 (25.5-127.5)	88 (54-163)	.058	51 (30,5-91)	99 (33.7-161.7)	.094
Remodeling index	3.4 (1.4-5.3)	2.3 (1.1-4.8)	4.1 (2.5-7)	.015	2.5 (1.1 -4.5)	4.1 (2.2-6.5)	.033
Number of plaques	3 (1-4)	2 (1-5)	3 (2-5)	.007	2 (1-4)	3 (2-5)	.075
Sum plaque score, 0-4	2 (0-4)	1 (0-4)	3 (0-4)	.023	1 (0-4)	3 (0-4)	.043
Segment involvement score, 1-16	3 (2-5)	2 (1-5)	4 (2-6)	.004	2 (1-4)	4 (2-6)	.005

Values are presented as absolute number (percentage), as mean ± standard deviation or as median (interquartile range).
**AU, indicates Agatston Uni*

Table 2.

Univariate regression analysis of hs-cTnT and NT-proBNP as dependent variables.

	r hs-cTnT	95% CI	*P* value	*r* NT-proBNP	95% CI	*P* value
Plaque volume, mm³	.256	0.05-0.44	.021	.270	0.06-0.46	.015
Calcified volume, mm³	.344	0.14-0.52	.002	.344	0.14-0.52	.002
Non-calcified volume, mm³	.050	-0.16-0.26	.660	.087	-0.13-0.29	.442
Burden, %	.267	0.06-0.45	.016	.276	0.07-0.46	.013
Remodeling index	.335	0.13-0.51	.002	.342	0.14-0.52	.002
Number of plaques	.355	0.15-0.53	.001	.301	0.09-048	.006
Sum plaque score, 0-4	.362	0.16-0.53	.001	.409	0.21-0.57	≤.001
Segment involvement score, 1-16	.320	0.11-0.49	.004	.355	0.16-0.53	.001

NT-proBNP levels (*r* hs-cTnT = .050; *r* NT-proBNP = .087; *P* value = .660 and *P* value= .442). The "Sum plaque score" was positively associated with both hs-cTnT and NT-proBNP concentrations (*r* hs-cTnT = .362; *r* NT-proBNP = .409; *P* value = .001 and *P* value ≤ .001) and thus showed the strongest correlation compared to other plaque parameters.

Figure 2 displays the relationship between hs-cTnT and NT-proBNP concentrations, total RI and number of plaques showing a progressive increase over the different quartiles.

Hs-cTnT and NT-proBNP concentrations showed a significant increase within three "Sum plaque score" categories as presented in Figure 3. As compared to category 1 ("Sum plaque score" 0 and 1), patients with a "Sum plaque score" of 4 had higher serum concentrations of hs-cTnT and NT-proBNP (both *P* values ≤ .001).

Follow-up and outcome

During a mean (± SD) follow-up period of 71 ± 7 months, 13 (16%) events occurred. ACS occurred in 11 patients (13.5%); CABG was performed in 2 patients (2.5%) at 16 and 28 months follow-up; no patients died due to cardiovascular causes. The distribution of events across "Sum plaque score", "Segment involvement score", hs-cTnT and NT-proBNP concentrations are presented in Table 3.

Hs-cTnT and NT-proBNP concentrations differed significantly between both "Sum plaque score" as well as "Segment involvement score" groups (all *P* values ≤ .027).

Interestingly, the number of events was higher in the second "Sum plaque score" (3-4) and "Segment involvement score" (4-16) group compared to the first group (9 (24%) versus 4 (9%)) with a trend towards statistical significance (both *P* values = .078).

FIGURE 2.

Hs-cTnT and NT-proBNP concentrations in relation to quartiles of total remodeling index (RI) (A, B) and total number of plaques (C, D). *Indicates statistical significance at *P* value ≤ .030 compared to quartile 1 (Total RI 1.4 and Total number plaques 2).

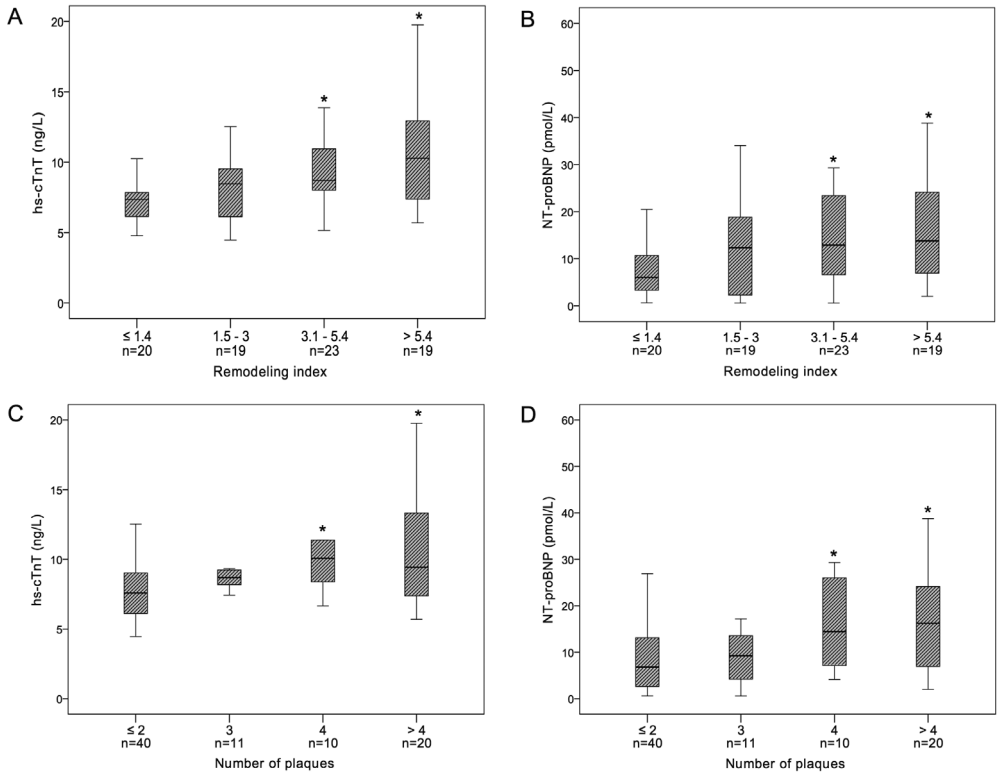


FIGURE 3.

A. Hs-cTnT and B. NT-proBNP concentrations in relation to "Sum plaque score" categories. Hs-cTnT and NT-proBNP concentrations show an increase with higher "Sum plaque score" categories. *Indicates statistical significance at *P* value ≤ .001 compared to the "Sum plaque score" 0 and 1 category.

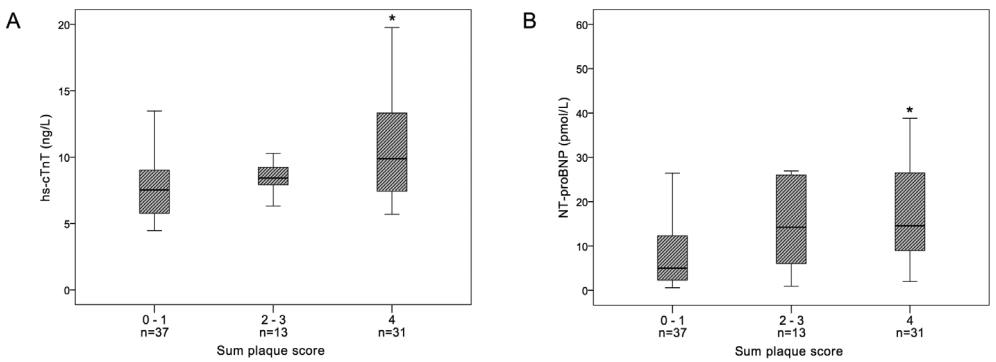


Table 3.

Distribution of events across "Sum plaque score" groups, "Segment involvement score", hs-cTnT and NT-proBNP concentrations.

CT-parameter	hs-cTnT (ng/L)	NT-proBNP (pmol/L)	Events
Sum plaque score			
0-2 n=43	7.6 (5.9-9)	5.3 (2.3-12.7)	4 (9)
3-4 n=38	9.2 (7.4-12.7)	14.4 (8.5-26.3)	9 (24)
Segment involvement score			
1-3 n=43	7.7 (6.7-9.2)	6.0 (2.3-12.3)	4 (9)
4-16 n=38	8.9 (7.3-11.9)	16.3 (8.3-26.5)	9 (24)

DISCUSSION

In the present study, we investigated the association of hs-cTnT and NT-proBNP with coronary atherosclerotic plaque characteristics derived by dedicated software in a hypothesis-generating setting. Our data indicate that hs-cTnT and NT-proBNP concentrations showed significant associations between total plaque volume, calcified volume, plaque burden, RI and number of plaques as well as the "Segment involvement score" defined by conventional coronary CTA reading.

The precise cause of cardiac troponin T (cTnT) release in patients with stable chest pain remains unclear in contrast to ACS patients in whom rupture of an atherosclerotic plaque with subsequent occlusive thrombosis causes prolonged myocardial ischaemia resulting in irreversible damage of the cardiomyocytes and thus cTnT leakage. One possible explanation of cTnT release in patients with stable chest pain is that plaque rupture can occur subclinically with subsequent microembolization leading to quantifiable levels of troponin (14-16). An alternative explanation for troponin leakage is demand ischemia. Intriguingly, in the present study, there was no association between stenosis severity and hs-cTnT. Coronary vasospasm as a reason for troponin release could not be excluded but is not very likely due to the usually short-term effect. Subclinical micro emboli may thus be a more plausible explanation for troponin release within the present study cohort due to the fact that plaque parameters were significantly associated with hs-cTnT and interestingly not with stenosis severity.

In addition to hs-cTnT, we also investigated the association between serum NT-proBNP concentrations and atherosclerotic plaque parameters. To our knowledge, this is the first study whereby significant associations were observed between NT-proBNP and coronary atherosclerotic plaque parameters, which was in accordance with the hs-cTnT findings. This observation could also be caused by induction of reversible myocardial ischemia due

to distal embolization with subsequent wall stretch in stable chest pain patients without known heart failure. Mair et al. already demonstrated, within a population who underwent CABG, a significantly enhanced brain natriuretic peptide release early during reperfusion of the human heart after global ischaemia, associated with cardioplegic cardiac arrest which also confirmed by Goetze et al. and Toth et al. (27-29). After all, myocardial ischemia can induce a reversible increase in regional wall stress that may lead to augmented natriuretic peptide release.

The fact that we did not found an association between non-calcified volume, hs-cTnT and NT-proBNP, while in literature this plaque phenotype is widely described as a coronary CTA defined high risk plaque feature, is uncontemplated (3, 4, 19). Korosoglou et al. previously showed a high correlation between hs-cTnT and non-calcified plaque volume suggesting that chronic silent rupture of non-calcified plaques with subsequent microembolization can lead to troponin leakage (14). However, important is to mention that this could have been influenced by the definition used for non-calcified plaques. Non-calcified plaques were namely defined as plaques with a calcified percentage ranging from 0% up to 80%, which was based upon a previous report (3). In contrast, we completely distinguished calcified from non-calcified volume whereby the total non-calcified plaque burden within the present study population was much lower in comparison to the calcified burden, which could also explain the lack of association between non-calcified volume, hs-cTnT and NT-proBNP.

To explore the associations more in depth, we created the "Sum plaque score" that included all plaque parameters resulting from the dedicated software. Our results showed that this score showed a strong positive association with hs-cTnT and NT-proBNP compared to the individual coronary plaque parameters. Additionally, we investigated the association of the "Segment involvement score" with hs-cTnT, NT-proBNP and outcome, showing significant associations between this generalizable scoring system and biomarkers. To our opinion, these findings support the use of a comprehensive coronary risk scoring system, which could incorporate novel coronary plaque quantification parameters and conventional coronary CTA parameters in addition to biomarkers. Consequently, coronary plaque parameters could reflect total vulnerable plaque material whereas cardiospecific biomarkers reflect disease activity. Such an approach could define vulnerability of the entire patient rather then of a single plaque, which has been previously suggested (30).

The main limitation of this study is the retrospective cross-sectional design whereby no direct causal relationships could be proven between hs-cTnT, NT-proBNP and the coronary plaque parameters. Secondly, the scoring system that was created ("Sum plaque score") is based on the results of the present study and thus further validation of such an approach in a prospective setting is needed. Finally, we selected an intermediate-to-high risk study cohort because this would be the relevant population to investigate possible associations between plaque parameters and biomarkers of myocardial injury and stress.

To our knowledge, the present study demonstrates for the first time a correlation between coronary CTA defined quantifiable unstable plaque characteristics and biomarkers of myocardial injury (hs-cTnT) and stress (NT-proBNP).

CONCLUSIONS

Our data suggest that plaque morphology parameters, derived by dedicated software, are associated with serum hs-cTnT and NT-proBNP concentrations. These data add to the injury and repair paradigm of plaque instability and thus could have an impact in future risk stratification of patients with stable chest pain.

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4

Chapter

Pericardial fat and its influence on cardiac diastolic function

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Abstract

BACKGROUND

Pericardial fat (PF) has been suggested to directly act on cardiomyocytes, leading to diastolic dysfunction. The aim of this study was to investigate whether a higher PF volume is associated with a lower diastolic function in healthy subjects.

METHODS

254 adults (40-70 years, BMI 18-35 kg/m^2, normal left ventricular ejection fraction), with (a)typical chest pain (otherwise healthy) from the cardiology outpatient clinic were retrospectively included in this study. All patients underwent a coronary computed tomographic angiography for the measurement of pericardial fat volume, as well as a transthoracic echocardiography for the assessment of diastolic function parameters. To assess the independent association of PF and diastolic function parameters, multivariable linear regression analysis was performed. To maximize differences in PF volume, the group was divided in low (lowest quartile of both sexes) and high (highest quartile of both sexes) PF volume. Multivariable binary logistic analysis was used to study the associations within the groups between PF and diastolic function, adjusted for age, BMI, and sex.

RESULTS

Significant associations for all four diastolic parameters with the PF volume were found after adjusting for BMI, age, and sex. In addition, subjects with high pericardial fat had a reduced left atrial volume index ($p=0.02$), lower E/e ($p<0.01$) and E/A ($p=0.01$), reduced e' lateral ($p<0.01$), reduced e' septal ($p=0.03$), compared to subjects with low pericardial fat.

CONCLUSION

These findings confirm that pericardial fat volume, even in healthy subjects with normal cardiac function, is associated with diastolic function. Our results suggest that the mechanical effects of PF may limit the distensibility of the heart and thereby directly contribute to diastolic dysfunction.

BACKGROUND

Diastolic heart failure is a major cause of morbidity and mortality (1) and is preceded by diastolic dysfunction, which is often present in patients with obesity and type 2 diabetes mellitus (T2DM). Diastolic dysfunction is defined as abnormal relaxation of the myocardium and may be present years before symptoms occur. It can be diagnosed by quantifying diastolic tissue motion and intracavitary filling pressures. The guidelines for diagnosing diastolic function combine measurement of diastolic tissue motion, diastolic blood flow quantification, and structural abnormalities such as the presence of left atrial dilation (2). Meeting 2 or more criteria results in the diagnosis of diastolic dysfunction.

Despite the clear definition, the understanding of the pathological mechanism of diastolic dysfunction remains poor. Various potential mechanisms have been suggested, but none of them can adequately explain the pathological process. Since increased pericardial fat (PF) volume is associated with adverse cardiovascular disease (CVD) outcomes, interest has peaked into this relationship and the potential effects of PF on cardiac dysfunction (3, 4).

PF is divided into two fat components: the Epicardial Adipose Tissue (EAT) and the Cardiac Adipose tissue (CAT). It is presumed that the EAT, due to its anatomical proximity to the myocardium, has the most effects on the myocardium. In normal physiology, EAT may have positive metabolic effects as it has an important function in lipid storing, and it also secretes endocrine factors (5). It demonstrates a great flexibility in the storage and release of fatty acids, which has been suggested to protect the heart from lipotoxicity, whilst simultaneously providing energy to the myocardium during high energy demand (6, 7). As a metabolically active endocrine organ, EAT also produces adipokines which may protect the heart from cardiovascular disease (8). However, when EAT expands, the balance between the storage and release of fatty acids shifts towards a more active secretion, as seen in obese subjects in comparison to lean subjects (9). The expanded EAT transforms its secretions into pro-inflammatory cytokines and chemokines (6, 8, 10). Cho et al. showed that the thickness of EAT at the right ventricle wall was associated with inflammation represented by hs-CRP level, LV mass, and subclinical myocardial dysfunction in males (11). This is also confirmed in EAT biopsies taken from patients undergoing coronary artery bypass grafting (CABG) (12, 13). Some of these mediators are known to have profibrotic properties, linking the inflammation of enlarged EAT with fibrosis (14). From studies performed in (morbidly) obese subjects with a high prevalence of T2DM, we know that PF, EAT, and CAT are linked to several diastolic function parameters (15-17). However, studies associating PF directly with diastolic function in healthy subjects are scarce, and the underlying mechanisms remain unknown (18-21).

Moreover, Ng et al. found an association between EAT volume index and interstitial myocardial fibrosis in an overweight to obese population (19). This association suggests that enlarged EAT may be related to asymptomatic cardiac remodeling, and hence, the enlarged

EAT may be involved in the development of cardiac diastolic dysfunction as is seen in overweighed subjects. Most studies on EAT have focused on the effects of EAT on systolic function, whereas in fact, in obese and diabetic populations, diastolic function are the first cardiac function parameters to change in obesity and metabolic syndrome (22). In addition, Yang et al. showed an increased EAT burden in pre-diabetic and diabetic subjects, compared to normoglycemic subjects (23). Also, Christensen et al. found that high levels of EAT were associated with the composite of incident CVD and mortality in subjects with T2DM (24). EAT may possibly play a more central role in the development of asymptomatic diastolic cardiac dysfunction than previously assumed, underlining the importance of a better understanding of the relationship between EAT and early changes in cardiac diastolic function. Hence, further studies focusing on exploring the relationship between EAT and diastolic dysfunction in a relatively healthy population, independently of their metabolic profile, are warranted.

In summary, it is unknown whether PF and / or EAT influences diastolic cardiac function in healthy subjects before any symptoms of diastolic failure occur. Most studies looking into the associations between PF or EAT with diastolic function have been performed in subjects with heart failure, CVD, overweight, or (pre-)diabetes (18-20, 25). This may possibly confound the relationship, as many structural and metabolic changes may interfere. Therefore, in this study, we aim to determine whether a higher PF volume is associated with subclinical but lower diastolic function in a healthy population. Secondly, we aim to examine if this lower diastolic function is solely derived from the EAT compartment, or if it is associated to the PF compartment as a whole.

METHODS

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) and Ethics Committee. Involved data were collected on a routine basis from within the Maastricht biomarker CT study (ClinicalTrials.gov NCT01671930, MEC 08-4-057) and analysed anonymously in accordance with Institutional Review Board guidelines. The study complies with the ethical principles of the Helsinki Declaration.

Study cohort

This study cohort is comprised of patients from the cardiology outpatient clinic presenting with (a)typical chest pain, who were according to the standard care protocol referred for coronary computed tomographic angiography (CCTA) for the evaluation of stable CVD, in accordance with the current guidelines (26, 27). Inclusion criteria for the Maastricht biomarker CT study were a recent history of cardiac typical or atypical chest pain, dyspnea, or collapse; at least 1 mL of serum for determination of biomarkers; and a diagnostic CCTA-scan, defined as 7 or more interpretable coronary segments. The exclusion criteria were hsCRP concentration >10 mg/L (indicating underlying inflammatory disease), severe renal dysfunction, or dialysis (due to application of contrast fluids).

254 patients enrolled in the echocardiography subgroup of the Maastricht Biomarker CT study were retrospectively included in this study (28, 29). A flowchart of inclusion is provided in Figure 1. In the present subgroup analysis (n=254), patients aged 40-70 years with a BMI between 18 and 35 kg/m^2 without history or diagnosis of acute coronary syndrome at the time of CCTA were included. Exclusion criteria for this subgroup study were: left ventricular ejection fraction (LVEF) <45%, diastolic dysfunction, atrial fibrillation, and diabetes mellitus.

Biochemical analysis

Serum samples were collected just before CCTA, processed within 2 hours and directly stored at -80°C until analysis. Total cholesterol (CV 2.0%), triglycerides (CV 2.5%), high-density (CV 3.0%) and low-density lipoprotein concentrations were measured as previously described (Cobas 6000, Roche Diagnostics) (28). Serum creatinine (CV 2.5%) and cystatin C concentrations were measured in a fresh aliquot (Cobas 6000; Roche Diagnostics). Creatinine concentrations were assessed using the enzymatic method (Cobas 6000, Roche Diagnostics). Cystatin C was measured using a new particle-enhanced turbidimetric assay (Gentian AS), which was standardized against the certified ERM-DA471/IFCC cystatin C reference material (30). Glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration equations using serum creatinine and cystatin C concentrations (31).

Cardiac computed tomographic angiography

All 254 patients had undergone a standardized non-enhanced scan to determine the calcium score using the Agatston method (32) at our center prior to CCTA assessment.

Semi-automatic segmentation determined the PF volume by dedicated software (SyngoVia, Siemens Healthineers, Forcheim, Germany) using a threshold from -150 to -50 Hounsfield Units to distinguish visceral adipose tissue, as set by the software (33). Because of the large sample size, only in a random sample of 10% of the subjects the pericardium was marked manually to separate the PF into EAT and CAT (depicted in Figure 2), and thereafter, the software calculated the separate 3D volumes of EAT and CAT.

Echocardiography

Echocardiography was performed within a period of 3 months from the CCTA by an experienced echocardiographist. Transthoracic images of the left ventricle (LV) were acquired to assess morphology, function and mass (Philips IE 33, Philips Healthcare). LV function and -mass were calculated by off-line analysis using Xcelera software package (Philips), according to current ESC/AHA guidelines (34).

Only four diastolic parameters are decisive in the evaluation of diastolic function according to the American Society of Echocardiography (ASE)/European Association of

FIGURE 1.

Flowchart of inclusion (n=254). **254 patients from the Maastricht biomarker CT study were eligible for the analysis of the association of PF and diastolic function in healthy subjects.**

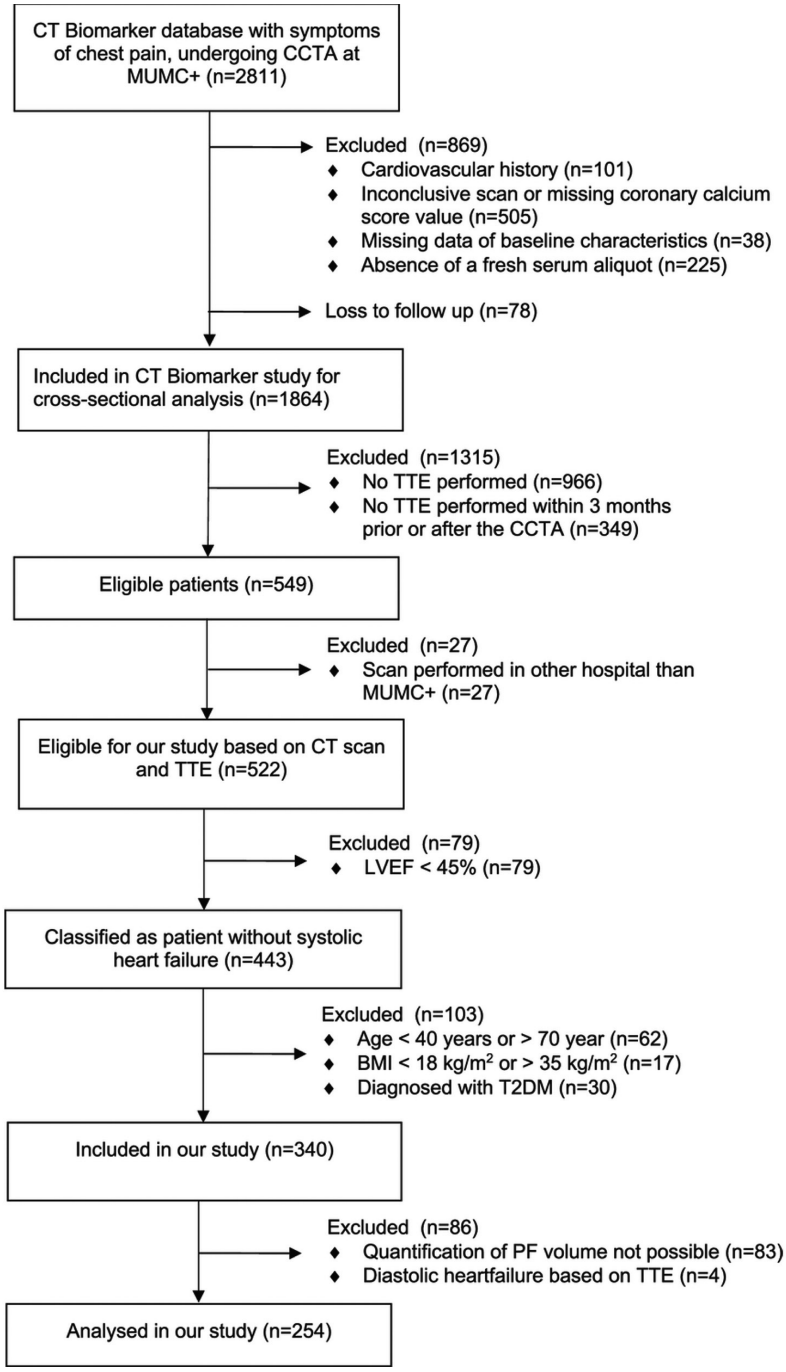
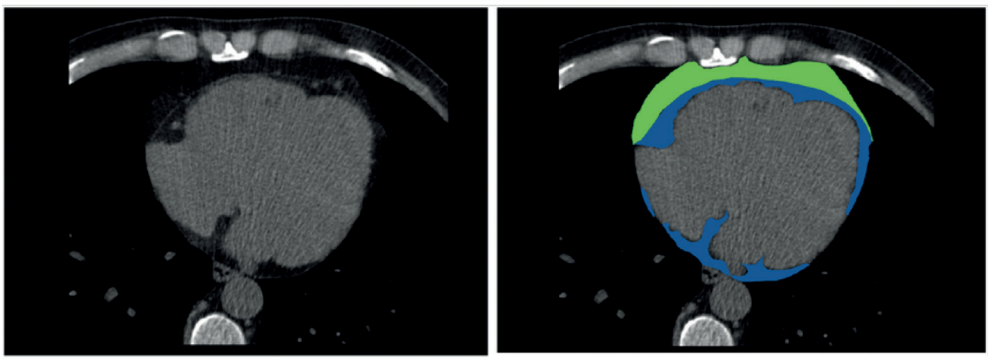


FIGURE 2.

Definition of pericardial fat (PF) and the related adipose tissues. **The adipose tissue surrounding the heart is defined as the pericardial fat (PF) and is a combination of epicardial and cardiac fat components. Within the PF, the pericardium demarcates the epicardial adipose tissue (EAT) from the cardiac adipose tissue (CAT). EAT (depicted in blue) is located between the myocardium and visceral pericardium, CAT (depicted in green) is located adherent and external to the parietal pericardium.**



Cardiovascular Imaging (EACVI) guidelines, namely, left atrial volume index (LAVI) , e' septal, e' lateral (mobility of the septal and lateral left ventricle wall respectively), and peak velocity of tricuspid regurgitation (TR) (2). Therefore, most of the analyses will focus upon these diastolic function parameters. But, in addition, also mitral peak A and E velocity, E/A ratio, and E/e' ratio, were determined.

Statistical analysis

Baseline characteristics of the sample were summarized using mean and standard deviation or median and interquartile range (IQR) for normally distributed and skewed continuous variables, respectively. Categorical data were presented as absolute number and percentage. To assess the independent association of PF and diastolic function parameters in these 254 patients, linear regression analysis was performed with either LAVI or e' septal or e' lateral or TR as the dependent variable. These models were adjusted for BMI, age, sex, and their interaction terms with PF, since it is known that these parameters are strongly associated with PF (9, 35, 36). Results of the linear regression analysis are presented as regression coefficient with 95% confidence interval (95% CI).

This study is based on a sample of healthy participants without diastolic dysfunction, therefore, only mild differences in diastolic function were expected. To maximize the differences in PF volume, the group was divided into low PF (lowest quartile of both sexes separately) and high PF (highest quartile of both sexes separately). The lowest and highest quartile groups were matched for cardiovascular risk factors, i.e., sex, systolic and diastolic blood pressure, total and LDL cholesterol, and kidney function. Differences in other baseline characteristics across these extreme quartiles of PF volume were investigated using the independent-samples t-test for continuous variables

with a normal distribution, or the Mann-Whitney U-test for non-normal distributed continuous variables. Pearson's chi-square test was used for categorical variables. Data are presented as proportions, means ± standard deviations, and data with a non-normal distribution are presented as the median (interquartile range, IQR).

To assess the independent association of PF and diastolic function parameters in these extreme quartiles (n=130), also multivariable linear regression analysis was performed with either LAVI, or e' septal, or e' lateral, or E/e', or TR as the dependent variable. These models were adjusted for BMI, age, and sex. Results are presented as regression coefficient with 95% confidence interval (95% CI).

To investigate the association of EAT with the total PF and EAT with diastolic function, Pearson's correlation coefficient was computed. Because only in 10% of the subjects an EAT volume was known, this subgroup was considered too small to perform regression analysis. All statistical analyses were performed with IBM SPSS Statistics Version 25.0 (SPSS, Inc.). Two-sided p-values of ≤ 0.05 were considered statistically significant.

RESULTS

The baseline characteristics for the total sample and the lowest and highest quartile groups of PF volume are presented in Table 1.

Distribution and determinants of the PF volume

Median (IQR) PF volume in the total cohort were 1.411 (IQR 1.035, 2.057) dl. Since males have a higher PF volume than females (median 1.729 dl, IQR 1.202,2.492; median 1.215 dl, IQR 0.909,1.552; respectively), the upper and lower PF volume quartiles of males and females were combined for the analysis (Figure 3A).

There was a significant difference between the lowest and highest quartile groups for age (55.7 ± 8.0 versus 59.1 ± 7.4, p = 0.015), BMI (23.7 ± 2.7 versus 28.1 ± 2.9, p value <0.001), glucose (5.5 ± 0.8 versus 5.9 ± 1.2, p = 0.025), HDL cholesterol (1.5 ± 0.4 versus 1.2 ± 0.4) and triglycerides (1.5 ± 1.1 versus 2.4 ± 2.0, p = 0.001), see table 1. The CAD findings were not different between the two groups of high and low PF. However, Framingham Risk Score was higher in the high PF group, possibly due to the association of PF with age and BMI.

Table 1.

Baseline characteristics of the study sample, and divided into highest and lowest quartiles of PF.

	Total sample ***(n=254)***	**PF low** ***(n=65)***	**PF high** ***(n=65)***	**P-value**
Demographics				
Age (years)	57.0 ± 7.5	55.7 ± 8.0	59.1 ± 7.4	0.015
Sex (% female)	48	46	48	0.860
Cardiovascular risk factors				
Framingham Risk Score	18.0 ± 13.2	14.4 ± 10.1	21.4 ± 16.1	0.004
Glucose (mmol/L)	5.6 ± 0.9	5.5 ± 0.8	5.9 ± 1.2	0.025
Body mass index (kg/m^2)	26.4 ± 3.7	23.7 ± 2.7	28.1 ± 2.9	<0.001
Systolic bloodpressure (mmHg)	142 ± 20	141 ± 23	146 ± 20	0.139
Diastolic bloodpressure (mmHg)	81 ± 11	80 ± 12	82 ± 11	0.254
Total cholesterol (mmol/L)	5.6 ± 1.1	5.5 ± 1.2	5.8 ± 1.2	0.148
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.5 ± 0.4	1.2 ± 0.4	0.001
LDL cholesterol (mmol/L)	3.6 ± 1.0	3.4 ± 1.0	3.6 ± 1.1	0.405
Triglycerides (mmol/L)	1.5 (1.0, 2.2)	1.2 (0.8, 1.5)	1.7 (1.3, 2.5)	<0.001
Creatinine (µmol/L)	76 ± 17	76 ± 15	75 ± 18	0.769
eGFR (MDRD) (ml/min/1.73m^2)	88 ± 18	89 ± 16	90 ± 21	0.619
CRP (mg/L)	2.3 ± 2.7	2.1 ± 2.5	2.8 ± 3.8	0.470
Coronary Artery Disease				
No Plaque (%)	39.4 ± 4.9	46.2 ± 5.0	35.4 ± 4.8	0.215
Mild (%)	37.0 ± 4.8	33.8 ± 4.8	36.9 ± 4.9	0.716
Moderate (%)	10.20 ± 3.0	7.7 ± 2.7	10.8 ± 3.1	0.548
Severe (%)	11.8 ± 3.2	9.2 ± 2.9	15.4 ± 3.6	0.289
Multi-vessel (%)	1.6 ± 1.3	3.1 ± 1.7	1.5 ± 1.2	0.563

Data are presented as means ± standard deviation, percentage, or as median (interquartile range, IQR).

FIGURE 3.

The variation of PF volume to sex, age and BMI in a healthy population. **PF volume is higher in males as in females (A), PF volume is not related to age (B) and PF volume is associated with BMI (C).**

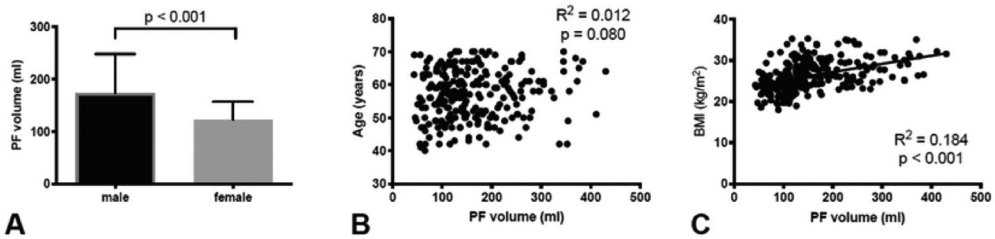


Table 2.

Cardiac function measured by transthoracic echocardiography.

	Total population ***(n=254)***	**PF low** ***(n=65)***	**PF high** ***(n=65)***	**P-value**
Left ventricular ejection fraction (%)	61 ± 5	62 ± 5	61 ± 5	0.213
Left ventricular mass index (g/m^2)	84.7 ± 16.9	80.6 ± 15.6	88.0 ± 16.0	0.008
Left atrial volume index (mL/m^2)	33.7 ± 0.7	36.8 ± 10.3	32.7 ± 8.4	0.015
e' lateral (cm/s)	11.0 ± 2.7	12.2 ± 2.9	10.3 ± 2.0	0.005
e' septal (cm/s)	8.5 ± 2.0	9.5 ± 2.1	8.4 ± 1.8	0.034
E/A	1.1 ± 0.4	1.1 ± 0.4	1.0 ± 0.4	0.013
Peak E velocity (cm/s)	72 ± 20	73 ± 24	70 ± 18	0.425
Peak A velocity (cm/s)	72 ± 18	66 ± 16	74 ± 17	0.004
E/e'	7.9 ± 2.1	6.8 ± 1.7	8.3 ± 2.3	0.009
Tricuspid regurgitation (m/s)	2.3 ± 0.4	2.2 ± 0.4	2.3 ± 0.3	0.416

Data are presented as means ± standard deviation. Reference values: LVEF >=45%, LAVI <34 ml/m^2, e' lateral >10 cm/s, e' septal >7 cm/s, E/A 0.8 – 2.5, E/e' 8 – 14, TR 2.0 – 2.8 m/s.

Distribution and determinants of diastolic function

The association between diastolic function and PF volume was investigated, as some of the diastolic parameters are expected to deteriorate during the development of diastolic dysfunction before clinical criteria for diastolic dysfunction are met (Figure 4).

Although still in the normal range, significant differences in the diastolic function parameters were found between the lowest and highest PF quartiles. As shown in table 2, a reduced LAVI and E/e' was found in the lowest PF quartile (p=0.02, p<0.01, respectively); and a reduced e' lateral, e' septal, and E/A in the highest PF quartile (p<0.01, p=0.03, p=0.01, respectively); and an increased peak A velocity in the highest PF quartile (p<0.01). Peak E velocity and TR did not differ significantly between the two extreme PF volume quartiles. Together, these differences reflect a diminished, although still normal, diastolic cardiac function in the highest PF quartile compared to the lowest PF quartile.

Association of PF with diastolic function

In the total sample (n=254), significant associations for all four diastolic parameters with the PF volume were found after adjusting for BMI, age, and sex. These data are depicted in Table 3. Analyses of the interactions with BMI, age, and sex, did not improve the model. In addition, in the extreme quartiles of PF volumes (n=130) a significantly negative association between high PF and LAVI, high PF and e' lateral, and high PF and TR, were found after adjusting for BMI, age, and sex. However, the difference in the mobility of the septal wall between the extreme quartiles of PF volume and between E/e' the extreme quartile of PF volume were no longer evident after the model was adjusted for these factors. These regression data are depicted in Table 4.

FIGURE 4.

PF is not associated with diastolic function parameters in a healthy population. **Data of the entire cohort (n=254) are displayed. No correlations are found.**

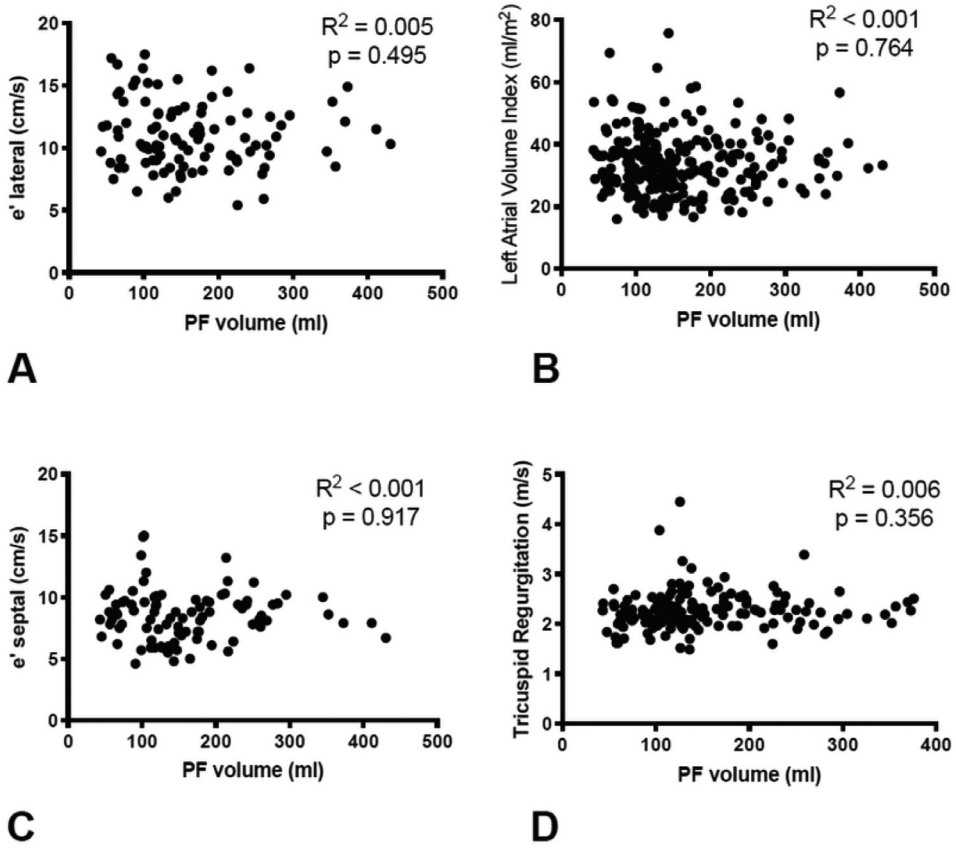


FIGURE 5.

No relation of PF to its CAT and EAT component. **The amount of CAT (A) and EAT (B) are not related to PF. Although EAT and CAT volume show a wide variation, they are linearly associated to each other (C), indicating that both increase with an increase of PF.**

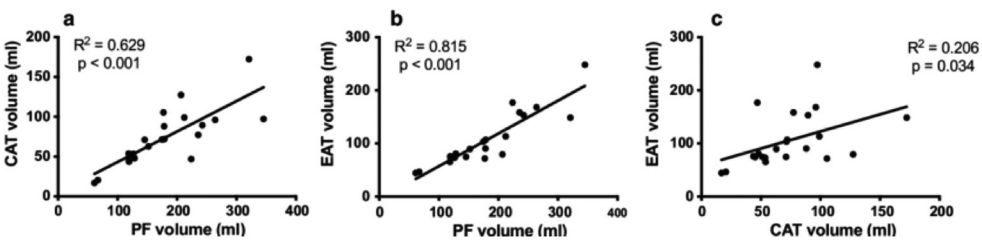


Table 3.

Multivariable linear regression analysis in the total population exploring associations between PF and parameters of diastolic cardiac function.

	Unadjusted regression coefficient (95% CI)	p-value	Adjusted regression coefficient * (95% CI)	p-value
Left atrial volume index (mL/m^2)	-0.24 (-1.79; 1.32)	0.764	-2.05 (-3.92; -0.19)	0.001
e' septal (cm/s)	-0.03 (-0.52; 0.47)	0.917	-0.13 (-0.68; 0.43)	0.020
e' lateral (cm/s)	-0.21 (-0.84; 0.41)	0.496	-0.02 (-0.71; 0.67)	<0.001
E/e'	7.45 (6.49; 8.42)	0.335	0.16 (-0.42; 0.74)	0.003
Tricuspid regurgitation (m/s)	0.04 (-0.04; 0.12)	0.356	-0.02 (-0.12; 0.07)	0.001

*Abbreviations: CI – confidence interval. * Adjusted for body mass index, age, and sex.*

Table 4.

Multivariable linear regression analysis in the extreme PF quartiles (0=low, 1=high) exploring associations between PF and parameters of diastolic cardiac function.

	Unadjusted regression coefficient (95% CI)	p-value	Adjusted regression coefficient * (95% CI)	p-value
Left atrial volume index (mL/m^2)	-4.13 (-7.47; -0.80)	0.015	-7.85 (-12.13; -3.56)	0.001
e' septal (cm/s)	-1.17 (-2.25; -0.10)	0.034	-0.96 (-2.28; 0.36)	0.088
e' lateral (cm/s)	-1.97 (-3.33; -0.60)	0.005	-1.39 (-3.13; 0.34)	0.020
E/e'	1.52 (0.40; 2.64)	0.009	1.33 (-0.11; 2.77)	0.118
Tricuspid regurgitation (m/s)	0.06 (-0.09; 0.22)	0.416	0.01 (-0.18; 0.20)	0.004

*Abbreviations: CI – confidence interval. * Adjusted for body mass index, age, and sex.*

Distribution and determinants of the different components of the PF volume

In 10% of the total sample (n=24), the EAT volume was studied by manually dividing the PF into the different CAT and EAT volumes. This random selection of 6 patients per PF quartile was made since the manual subdivision of the PF is extremely laborious, and to ascertain that the sample reflects the entire population. The data showed that with an increasing PF, no similar increase in the relative volume of EAT and CAT can be expected, as the relationship with the relative amount of EAT and CAT is lacking (p>0.7). These data are illustrated in Figure 5.

To gain further insight into whether EAT is the major culprit in hampering diastolic function as suggested because of its anatomic proximity to the myocardium, separate correlations of EAT were made with the different diastolic parameters. Despite the small number, a direct correlation of the percentage of EAT and e' lateral was found. There was no correlation with EAT and the other diastolic function parameters (Figure S4 in the Supplementary Appendix).

DISCUSSION

Studies associating PF or EAT with diastolic function are scarce and often contradictive. A partial explanation may be that most studies so far were performed in a non-healthy population, which may confound the reported associations of PF or EAT with diastolic function (15-20). Here, we studied the association between PF and diastolic function in a lean to obese middle-aged population, with normal systolic and diastolic cardiac function. We evaluated these relationships independently of their metabolic profile as correction for metabolic risk factors was applied. Furthermore, we explored the association of EAT with PF and EAT with diastolic function.

We report that PF was significantly associated with the diastolic function parameters LAVI, e' lateral, e' septal, E/e', and TR, when corrected for age, BMI, and sex. Adjustment for sex alone was already sufficient to render the association significant, since PF is different distributed between male and female. The reported associations indicate that even in our healthy population with a normal diastolic function, PF – independently of CVD risk factors related to age, BMI, and sex – is associated with diastolic function parameters.

In the analyses focusing on low and high PF volume, high PF was associated with a decrease in LAVI and e' lateral, and an increase in TR (as depicted in Figure 5). The decrease in e' lateral is in line with previous research performed in (morbid) obese subjects with a high prevalence of T2DM (15). The lower e' lateral in the highest PF quartile reflects a slower relaxation of the lateral wall of the left ventricle, necessary for an effective diastolic filling phase. The lower LAVI in the highest PF quartile is not known to be a sign of lower diastolic function. We do not know what underlies these findings, but they may indicate that PF causes mechanical hindrance that compromises not only the mobility of the lateral left ventricle wall (e' lateral), but also compresses the left atrium, and thereby reducing its volume (LAVI). This hypothesis needs further work.

Although EAT was only determined in a small subpopulation (n=24), insights in the compartmental distribution of PF and its consequences on diastolic function can be gathered. We found that at increased PF volumes, the EAT and CAT compartments increased at a same amount relatively to the whole fat depot. This is surprising as Wu et al. reported that subjects after bariatric surgery showed a great loss of CAT and only a small decrease in EAT (37). Therefore, the regional distribution of adipose tissue remains an important subject for further research, taking into account that this distribution plays an important role in the development of metabolic syndrome and CVD (38).

The association of high PF with e' lateral suggests that in a healthy population the mechanical effects of PF limit the distensibility of the heart first, which subsequently contributes to diastolic dysfunction. This study suggests that secondly, after progression of this relaxation problem of the lateral wall, the LAVI might increase despite the compression of the PF mass, as seen in diastolic dysfunction. But this remains speculative, as we did not measure the mobility of the lateral wall of the left

ventricle during the systolic phase. However, during systole the PF mass will be less restrictive than during diastole, which is in line with our hypothesis. Most notably, a mechanically limited heart is accompanied by pressure changes within the cardiomyocytes, which in turn can affect the metabolism of these cells, and thereby, negatively influence diastolic function.

Most of the research on PF so far focused on adipokine release and a potentially causal role in the formation of fibroses. Pressure changes due to increased PF leading to an altered metabolism are an alternative pathway how PF can influence cardiac function. Thus, although the underlying mechanism remains unknown, the idea that mechanical effects of high PF cause a diminished mobility of the myocardium is supported by the current data. As others already suggested, this diminished mobility may provoke fibrosis, which has been associated with diastolic dysfunction, however this remains to be elucidated. In our population changes in diastolic function parameters were associated with an increase in PF, however, the diastolic function was within normal range; hence no causality with fibrosis could be made.

LIMITATIONS

As we performed a cross-sectional retrospective study, our study has some limitations by design. Due to the retrospective design, the low and high PF groups were not matched on all relevant characteristics. However, we did adjust our analyses for age, BMI, and sex. Although we corrected for age, BMI, and sex, some of metabolic characteristics such as glucose, HDL-cholesterol, and triglycerides, may confound the associations, although these metabolic characteristics were within normal range. Also, because of the retrospective design, there was timeframe of a maximum of three months between the CCTA and TTE, this may have influenced our association. In addition, since the manual subdivision of the PF is extremely laborious, we only separated the PF components in 10% of the total cohort, following random selection. Thus, the power was limited for exploring the metabolic effects of EAT, independently of PF, on diastolic function. The cross-sectional outline of this study does not allow any conclusions regarding possible causality. Future work should therefore include a prospective approach to evaluate causal relationships.

Finally, it is important to bear in mind that our study population consisted of relatively healthy subjects, whose cardiac diastolic function was considered to be good. We only studied the associations between PF and small variations in normal diastolic function, which also explains why we did not find correlations between the diastolic parameters and age, BMI, or sex, in our sample (Figures S1, S2, S3 in the Supplementary Appendix). There were no subjects with clinically defined diastolic failure to assess the relationships between PF and diastolic dysfunction. This, of course, remains an important question for future research.

CONCLUSION

The purpose of the current study was to determine the association of PF and cardiac diastolic function in a healthy population. Linear regression analysis revealed that PF, independently of age, BMI, and sex, is associated with the four diastolic ultrasound parameters which are decisive in the evaluation of diastolic function. A potential underlying mechanism of this may be that increased PF may compress the heart, leading to a limited distensibility in the diastole and fibrosis as seen in cardiac remodeling, and thus, may lead to diastolic dysfunction. This study adds to the growing body of research that explores possible mechanisms in the development of diastolic failure. Concluding, we confirm that PF, even in healthy subjects with normal cardiac function and without diabetes, does hinder diastolic function. The exact causality of this effect and the relationship with fibrosis remains to be determined.

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Supplementary
FILES

FIGURE S1.

Associations between BMI and diastolic function parameters in a healthy population. **BMI is negatively associated with e' lateral (A), but not with LAVI (B), e'septal (C) or TR (D) in a healthy population.**

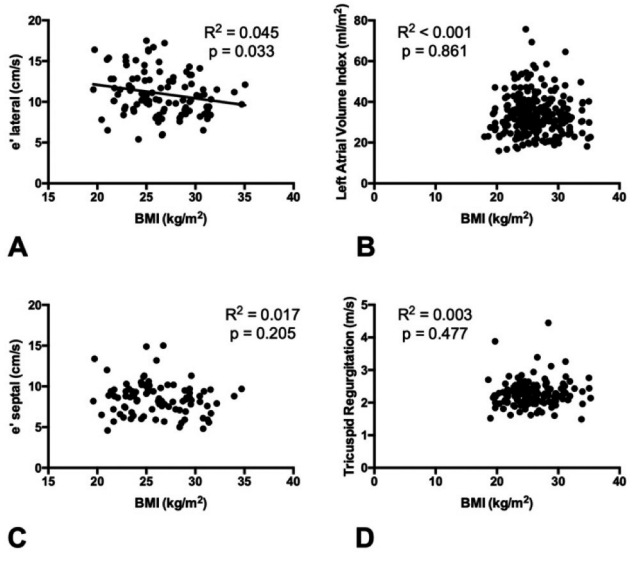


FIGURE S2.

Associations between age and diastolic function parameters in a healthy population. **Age is negatively associated with e' lateral (A), and positively associated with TR (D) in a healthy population. Age is not associated with LAVI (B), nor with e' septal (C).**

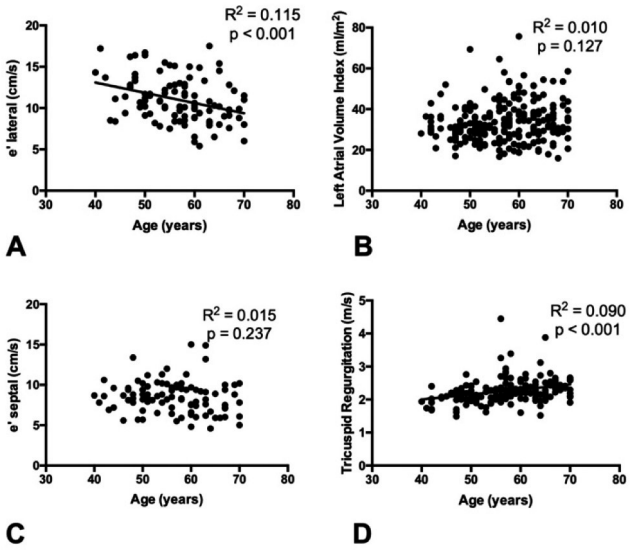


FIGURE S3.

Associations between sex and diastolic function parameters in a healthy population. **Males are associated with higher e' lateral (A), higher LAVI (B), and higher e' septal (C), compared to females. No sex difference is observed in TR (D).**

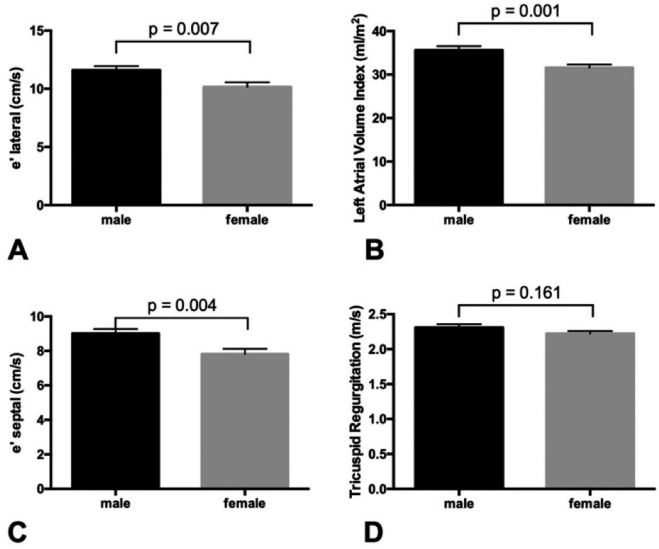
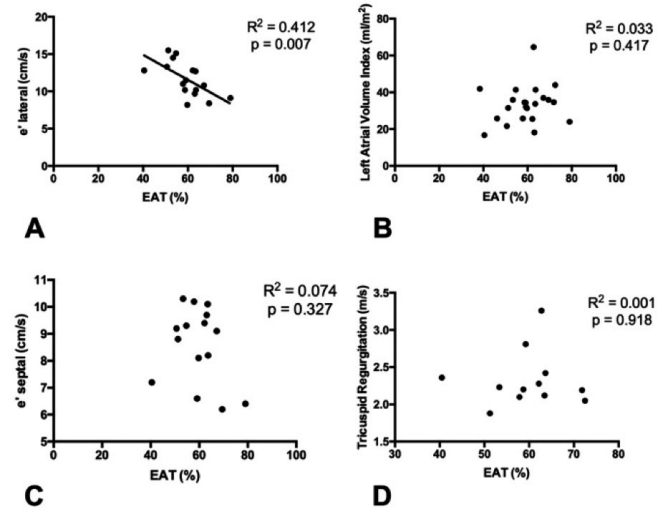


FIGURE S4.

Associations between EAT volume (as % of PF volume) and diastolic function parameters in subjects with low or high PF volume within a healthy population. **Only e' lateral (B) was associated with the relative amount of EAT volume; no associations were found for LAVI (B), e' septal (C), nor TR (D).**



Chapter

Presence and extent of cardiac computed tomography angiography defined coronary artery disease in patients presenting with syncope

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Abstract

BACKGROUND

In syncope patients, presence of coronary artery disease (CAD) is associated with poor prognosis. However, data concerning CAD prevalence in syncope patients without known cardiovascular disease are lacking. Therefore, the aim of this study was to investigate presence and extent of CAD in syncope patients.

METHODS

We included 142 consecutive patients presenting with syncope at the outpatient cardiology clinic who underwent coronary computed tomography (CT) angiography. Syncope type was ascertained by two reviewers, blinded for coronary CT angiography results. Of the 49 patients had cardiac (arrhythmia or structural cardiopulmonary disease) and 93 had non-cardiac syncope (reflex syncope (neurally-mediated), orthostatic syncope or syncope of unkown cause). Cardiac syncope patients were compared with matched stable chest pain patients regarding age, gender, smoking status, diabetes mellitus type 2 and systolic blood pressure.

RESULTS

Distribution of CAD presence and extent in cardiac and non-cardiac syncope patients was as follows: 72% versus 48% any CAD; 31% versus 26% mild; 8% versus 14% moderate and 33% versus 7% severe CAD.

Compared with non-cardiac syncope, patients with cardiac syncope had a significantly higher CAD presence and extent (p= 0.001). Coronary calcium score, segment involvement and stenosis score were also higher in cardiac syncope patients (p-values ≤0.004). Compared to chest pain control group, patients with cardiac syncope showed a higher, however, non-significant, prevalence of any CAD (72% versus 63%) and severe CAD (33% versus 19%).

CONCLUSION

Patients with cardiac syncope show a high presence and extent of CAD in contrast to non-cardiac syncope patients. These results suggest that CAD may play an important role in the occurrence of cardiac syncope.

INTRODUCTION

Syncope is defined as a transient loss of consciousness due to transient global cerebral hypoperfusion and is characterized by a rapid onset, short duration and complete spontaneous recovery (1, 2). It concerns a common medical problem, with an incidence rate of 6.2 per 1000 person-years for a first report (3). Syncope is a symptom with a wide spectrum of potential etiologies wherefore accurate diagnosis, using additional testing, is of high importance (4-6). Along with the search for the underlying diagnosis, defining prognosis is crucial whereby the risk of death, recurrence as well as life-threatening events should be considered (2, 4).

Within the current European Society of Cardiology Guidelines for the diagnosis and management of syncope, only limited guidance is offered for diagnostic strategies to detect CAD (2). Ischemia evaluation is recommended within the current guidelines of the American College of Cardiology/American Heart Association (ACC/AHH) for syncope patients with known or who are at risk for coronary artery disease (CAD) (6). However, there is no guidance regarding anatomical imaging techniques to detect CAD in syncope patients despite the evidence that arrhythmic causes for syncope, such as atrial fibrillation or ventricular tachycardia, have a higher risk of major adverse cardiovascular and cerebral events in the presence CAD (7, 8). Additionally, all patients with syncope and ischemic heart disease have an increased risk of death (1, 3, 9).

Currently, coronary CT angiography (CCTA) is a widely implemented non-invasive imaging modality to diagnose CAD (10-12). Conventional CCTA reading includes assessment of the coronary calcium score (CCS), luminal stenosis severity and extent of CAD with high sensitivity and specificity (10, 12). It may be considered in stable chest pain patients with an intermediate pretest probability of ischemic heart disease (13). Despite of the wide use of CCTA in patients with stable chest pain, there are no recommendations for CAD detection with CCTA in patients presenting with syncope. Nevertheless, diagnosing CAD within syncope patients in an early stage could have important prognostic and therapeutic clinical implications. Therefore, the aim of the present study was to investigate the presence and extent of CAD, as defined by CCTA, in patients presenting with syncope at the outpatient cardiology clinic.

METHODS

Study population

This was an observational single-center study analysing 142 retrospectively collected consecutive patients presenting with syncope between May 2007 and April 2015 at the outpatient cardiology department and who were referred for CCTA within their diagnostic workup. Patients were selected if they met the definition of syncope, which was defined as transient loss of consciousness due to global cerebral hypoperfusion with rapid onset, short duration and spontaneous complete recovery (2).

General exclusion criteria for CCTA examination were: hemodynamic instability, pregnancy, renal insufficiency (defined as glomerular filtration rate <45mL/min/1.73m) and known severe allergic reactions concerning iodine.

This study was approved by the Institutional Review Board (METC 15-4-091) and complies to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was waived because the data were anonymously recorded and analyzed in accordance with guidelines of our Review Board.

Data collection and definitions

Data regarding syncope type, age, gender, cardiovascular risk factors, medication use, additional diagnostic testing and CCTA results were collected from the patient charts and electronic medical records.

The type of syncope was ascertained by chart review by two reviewers (N. M., T. D.), blinded for CCTA results. The definitive syncope type was ascertained by consensus between the two reviewers. The following pathophysiological *classification* and sub-classification was used to adequately define the syncope types in each individual patient (2):

1. *Cardiac syncope (cardiovascular)*: arrhythmia or structural cardiopulmonary disease as primary cause;
2. *Reflex (neurally-mediated) syncope*: vasovagal, situational or carotid sinus syncope;
3. *Syncope due to orthostatic hypotension*: primary or secondary autonomic failure, drug-induced orthostatic hypotension or volume depletion;
4. *Syncope of unkown cause:* defined as an unknown cause despite additional diagnostic testing.

Subsequently, patients with *reflex syncope*, *orthostatic syncope* and *syncope of unkown cause* were classified as having "non-cardiac syncope" which led to two main syncope categories: *cardiac* and *non-cardiac syncope*.

Diabetes mellitus was defined as fasting glucose levels of ≥7 mmol/L or treatment with either diet intervention, oral glucose lowering agent or insulin (14); smoking was defined as current smoking. A positive family history was defined as having a first-degree relative with a history of myocardial infarction or sudden cardiac death before the age of sixty.

The PROCAM risk score was determined according to the following parameters: age, LDL cholesterol, smoking, HDL cholesterol, systolic blood pressure, family history of premature myocardial infarction, diabetes mellitus, and triglycerides (15). This risk score predicts the absolute 10-year risk for the occurrence of an acute coronary event (fatal or non-fatal myocardial infarction or acute coronary death). A score <10% is estimated as low risk, 10-20% intermediate, and >20% as high risk.

Control population

To further study the impact of cardiac syncope symptoms on detection of CAD, we compared the cardiac syncope patients with stable chest pain patients. The cardiac syncope patients were compared (1:2 ratio) with stable chest pain patients, referred for

CCTA from the outpatient cardiology clinic in order to compare the prevalence and extent of CAD in cardiac syncope patients with stable chest pain patients. Matching was based upon age, gender, smoking status, diabetes mellitus type 2 and systolic blood pressure (±10mmHg).

CCTA acquisition

Scans were performed using a 64-slice multidetector computed tomography scanner (Brilliance 64; Philips Healthcare, Best, The Netherlands) or a 2nd generation dual-source CT-scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). Data acquisition parameters for the Brilliance 64 were a 64 x 0.625 mm slice collimation, a gantry rotation time of 420ms and a tube voltage of 80 or 120 kV which depending on patients' height and weight. Data acquisition parameters for the Somatom Definition Flash were a 2 x 128 x 0.600 mm slice collimation, a gantry rotation time of 280 ms and a tube voltage of 100 or 120 kV depending on patients' height and weight. A non-contrast enhanced scan was performed using 120 kV and 3 mm slice thickness to determine the CCS [16]. CCTA was performed using 75-120 mL of contrast agent (Xenetix 350; Guerbet, France or Ultravist 300; Bayer Healthcare, Berlin, Germany), which injected in the antecubital vein at a rate of 5.2-7.4 mL/s followed by 40mL intravenous saline at the same flow rates.

Scan protocols differed between both CT-scanners. For the 64-slice scanner, a prospectively gated "Step and shoot" protocol was used in patients with stable heart rate <65 bpm. In patients with a heart rate >65 bpm, a retrospectively gated "Helical" protocol was used with dose modulation. For the 2nd generation dual-source CT-scanner, a prospectively gated high-pitch spiral "Flash" protocol was used in patients with a stable heart rate <60 bpm. In patients with a stable heart rate between 60-90 bpm, a prospectively gated axial "Adaptive sequence" protocol was used. In patients with a heart rate >90 bpm or in case of an irregular heart rhythm, a retrospectively gated "Helical" protocol was used. Dose modulation was switched on in all three protocols using tube current modulation (CARE Dose4D, Siemens Healthcare, Forchheim, Germany).

Patients received 50 mg Metoprolol tartrate orally (AstraZeneca, Zoetermeer, the Netherlands), two hours before CCTA, unless contra-indicated. If indicated, an additional dose of 5-20 mg Metoprolol was administered intravenously to lower the heart rate. All patients received nitroglycerin (Pohl-Boskamp, Hohenlockstedt, Germany) sublingually in a dose of 0.8 mg just prior to CCTA.

CCTA assessment

The Agatston method was used to define the CCS (16). CCTA's were independently analyzed by a cardiologist and a radiologist, both experienced in the assessment of CCTA. In case of disagreement, consensus was reached by discussion. The assessment was performed using the source images on the provided software (Cardiac Comprehensive Analysis, Philips Healthcare or Syngo CT 2010A, Siemens Healthcare).

The coronary artery tree was analyzed for the presence and extent of CAD, according to the 16-segment classification of the American Heart Association (17). Plaques were defined as visible structures within or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue. The degree of stenosis was visually defined and classified as no CAD (no luminal stenosis), mild (<50% luminal stenosis), moderate (50-70% luminal stenosis), severe (>70% luminal stenosis). A segment involvement score was defined by counting all coronary segments with plaques (irrespective of degree of stenosis), which resulted in a score ranging from 0-16 (18). A segment stenosis score was the sum of the lesion severity in all 16-coronary segments resulting in a score ranging from 0-48 (18).

Statistical analysis

Data were analysed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were checked whether they were normally distributed using box plots, histograms and by computing skewness and kurtosis. Continuous data were reported as means and standard deviations (SD) if normally distributed. If data were not normally distributed, continuous data were reported as medians and boundaries of interquartile ranges (IQR). Proportions (%) were used for categorical values.

Differences across groups were assessed using the independent *t*-test for normally distributed data after performing Levene's test for equality of variance. The Mann-Whitney test was used for data, which were not normally distributed. Categorical variables were tested with Fisher's exact test.

All P-values were 2-sided, and a P-value below 0.05 was considered statistically significant.

RESULTS

Study population

Between May 2007 and April 2015, 142 consecutive patients presented with syncope at the outpatient cardiology clinic who were referred for CCTA. The distribution of syncope classifications was as follows: 49 (35%) cardiac, 63 (44%) reflex (neurally-mediated), 10 (7%) orthostatic hypotension and 20 (14%) syncope of unkown cause. Subsequently, patients with reflex syncope, orthostatic syncope and syncope of unkown cause were classified as having "non-cardiac syncope" leading to two main categories, with 49 (35%) cardiac syncope patients and 93 (65%) non-cardiac syncope patients.

The baseline characteristics of the study population are described in *Table 1*. When compared to non-cardiac syncope patients, only age showed a statistically significant difference between the cardiac and non-cardiac syncope groups (mean (SD): 60 (13) versus 54 (12); p=0.002). *The Online Supplemental Appendix* provides further detailed clinical information regarding to the syncope patients.

Table 1.

Baseline characteristics of the study population.

	Cardiac syncope vs. non-cardiac syncope *n=142*			**Cardiac syncope vs. chest pain control group *n=147***		
Patient characteristics	***Cardiac syncope n=49***	***Non-Cardiac syncope n=93***	***P-value***	***Cardiac syncope n=49***	***Chest pain Control group n=98***	***P-value***
Age, *years*	60 ± 13	54 ± 12	**0.002**	60 ± 13	60 ± 12	0.810
Male gender	32 (65)	57 (61)	0.716	32 (65)	64 (65)	>0.999
BMI, *kg/m²*	26 ± 3	26 ± 4	0.365	26 ± 3	27 ± 4	0.116
Systolic Blood Pressure, *mmHg*	143 ± 20	140 ± 21	0.349	143 ± 20	144 ± 16	0.990
Diastolic Blood Pressure, *mmHg*	81 ± 13	83 ± 13	0.396	81 ± 13	78 ± 9	0.140
Active smoking	19 (39)	27 (29)	0.256	19 (40)	38 (39)	>0.999
Diabetes mellitus II	3 (6)	4 (4)	0.693	3 (6)	5 (5)	>0.999
Family history of CAD	16 (33)	43 (46)	0.152	16 (33)	27 (28)	0.566
PROCAM risk score	9 (4 – 21)†	7 (2 – 16)‡	0.131	9 (4 – 21)†	8 (3-16)	0.280

BMI: body mass index. Continous variables are described as mean (± SD) or as median (interquartile range); categorical variables as number (%). † n=19 lost for PROCAM risk score. ‡ n=34 lost for PROCAM risk score.

Presence and extent of CAD in syncope

The distribution of CAD presence and extent in cardiac and non-cardiac syncope patients was as follows: 72% versus 48% any CAD; 31% versus 26% mild CAD; 8% versus 14% moderate CAD and 33% versus 7% severe CAD *(Table 2)*.

Figure 1 visualises CAD prevalence and distribution of CAD in patients with cardiac and non-cardiac syncope. CAD presence and extent was significantly higher in patients with cardiac syncope in comparison with non-cardiac syncope patients (*Table 1; p=0.001*). Additionally, all conventional CT-parameters including CCS, segment involvement and segment stenosis score were significantly higher in patients with cardiac syncope compared to non-cardiac syncope (80 [0-387] versus 0 [0-79]; 2 [0-5] versus 0 [0-2]; 3 [0-7] versus 0 [0-3]) (all p-values ≤0.004; *Table 2*).

FIGURE 1.

CAD presence and extent (percentages) within cardiac syncope patients versus non-cardiac syncope patients.

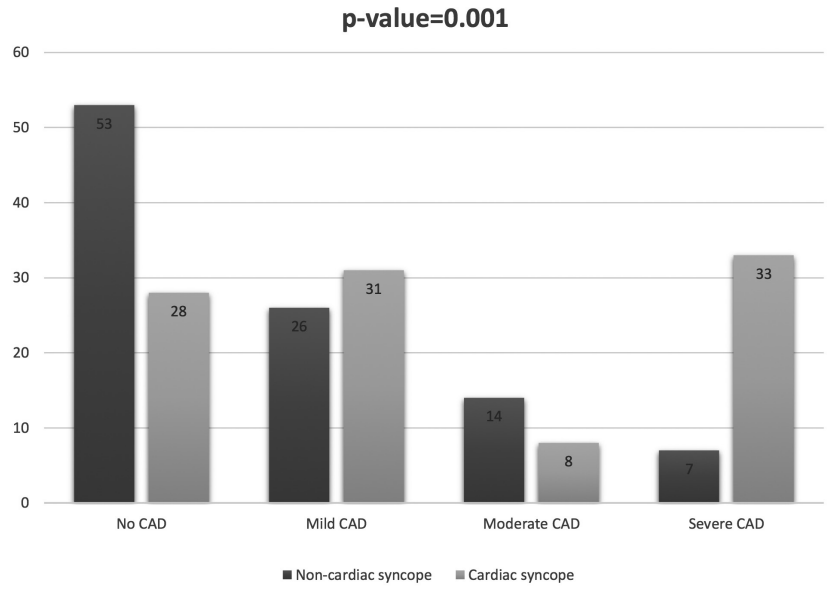
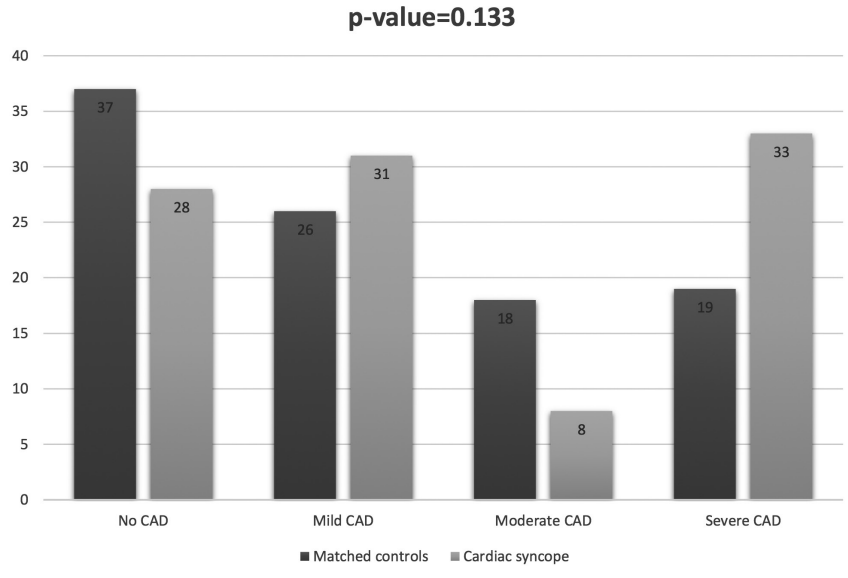


FIGURE 2.

CAD presence and extent (percentages) within cardiac syncope versus matched chest pain controls.



Presence and extent of CAD in patients with cardiac syncope versus matched chest pain controls

Figure 2 displays the presence and extent of CAD in both cardiac syncope patients and matched chest pain controls. Patients with cardiac syncope showed a higher prevalence of any CAD (72% versus 63% respectively) and percentage of severe luminal stenosis (33% versus 19%). Interestingly, no statistically significant difference was observed between cardiac syncope patients and chest pain controls regarding overall prevalence of CAD presence and its extent (p=0.133). Shows that all other conventional CT-parameters including CCS, segment involvement score and segment stenosis score were comparable between cardiac syncope patients and chest pain controls (all p-values ≥0.272).

Table 2.

Distribution of conventional CT parameters across cardiac syncope patients versus non-cardiac syncope patients and matched chest pain control group

	Cardiac syncope vs. non-cardiac syncope *n=142*			**Cardiac syncope vs. chest pain control group *n=147***		
CT-parameters	***Cardiac syncope n=49***	***Non-cardiac syncope n=93***	***P-value***	***Cardiac syncope n=49***	***Chest pain Controls n=98***	***P-value***
Presence and extent of CAD			0.001			0.133
No CAD	14 (28)	49 (53)		14 (28)	36 (37)	
Mild CAD, *<50% luminal stenosis*	15 (31)	24 (26)		15 (31)	25 (26)	
Moderate CAD, *50-70% luminal stenosis*	4 (8)	13 (14)		4 (8)	18 (18)	
Severe CAD, *>70% luminal stenosis*	16 (33)	7 (7)		16 (33)	19 (19)	
Coronary calcium score, *AU*	80 (0-387)	0 (0-79)	0.002	80 (0-387)	36 (0-205)	0.272
Segment involvement score, *0-16*	2 (0-5)	0 (0-2)	0.004	2 (0-5)	2 (0-4)	0.364
Segment stenosis score, *0-48*	3 (0-7)	0 (0-3)	0.003	3 (0-7)	2 (0-7)	0.477

CT: computed tomography; CAD: coronary artery disease.

DISCUSSION

To our best knowledge, this is the first study dedicated to investigating the prevalence and extent of CAD in patients presenting with syncope. The main finding of this study was that cardiac syncope patients showed a high presence and extent of CAD in comparison with non-cardiac syncope patients. In addition, all other coronary CT-parameters like CCS, segment involvement score and stenosis score were also significantly higher in cardiac syncope patients compared to non-cardiac syncope patients. When compared to stable chest pain controls, patients with cardiac syncope showed a higher, however, non-significant, prevalence of any CAD (72% versus 63% respectively) and percentage of severe luminal stenosis (33% versus 19%). Taken together, these results suggest that the non-invasive evaluation of CAD, using CCTA could be considered within the diagnostic workup of patients presenting with cardiac syncope at the outpatient cardiology clinic. Additionally, CCTA may show alternative causes for cardiovascular syncope such as congenital anomalies of coronary arteries, hypertrophic cardiomyopathy, pulmonary embolism, obstructive valvular disease, intracardiac masses and pericardial diseases.

Association and relevance of CAD in cardiac syncope

Meticulous history taking is essential in arriving at a diagnosis in patients with syncope. Once cardiac syncope is suspected, a wide range of different diagnostic tests can be considered in patients presenting with syncope (2, 6). However, there is no guidance regarding anatomical imaging techniques to detect CAD due to lacking evidence describing the extent and nature of CAD in patients with cardiac syncope. The relationship between cardiac ischemia and syncope is multiple, including induction of nonsustained ventricular arrhythmias and sinoatrial or atrioventricular block, or by triggering e.g. the Bezold-Jarisch reflex causing severe bradycardia and hypotension. Apart from a direct relationship, indirect mechanisms may be important, including old myocardial infarction with ventricular remodeling as a basis for reentrant or adrenergic ventricular tachycardia; likewise, atrial remodeling leading to late onset atrioventricular nodal tachycardia or atrial tachycardias may at times occur with well-known hemodynamic compromise eliciting syncope at the beginning of the attack (19). In all of the above-mentioned etiologies, CAD may be causal or contributory for syncope whereby one could conjecture that interventional and vascular prophylactic management may help to reduce further syncope in these patients. In all other cases, CAD presence should be considered as coincidental wherefore vascular prophylactic vascular management may not be indicated in the management of syncope.

Current guidance for the detection of CAD in cardiac syncope

Within the European Society of Cardiology guidelines for the diagnosis and management of syncope, exercise stress testing is only recommended in patients with suspected exercise-induced syncope, which concerns a rare condition (2). Concurrently, ischemia evaluation is

recommended by the American College of Cardiology/American Heart Association (ACC/AHA) for patients with syncope and an intermediate-to-high risk for coronary heart disease or known CAD, but such strategy may underdiagnose the presence of non-obstructive CAD, which still is associated with high major adverse cardiac event rates (6, 20, 21). On the other hand, a previous report revealed a low-diagnostic yield for stress myocardial perfusion imaging across all risk categories in syncope patients without known CAD (22).

Prior studies

Previously, Soteriades et al. investigated the incidence and prognosis of syncope among participants of the Framingham Heart Study and found that patients with a cardiac syncope were more likely to have a history of CAD and were at increased risk for death from any cause and cardiovascular events (3). A more recent study of patients presenting with syncope at the emergency department with trauma, have shown that patients with a history of CAD are four times more likely to have cardiac syncope in contrast to non-cardiac syncope (23).

These previous reports support the high prevalence and extent of CAD in patients presenting with cardiac syncope compared to patients with non-cardiac syncope within the present study. Furthermore, in the presence of obstructive CAD in patients with syncope, treatment by either percutaneous coronary intervention (PCI) or medical management did not improve readmission rates due to syncope. However, PCI did improve long-term mortality in patients with syncope, suggesting the need for imaging of the coronary arteries (24).

Moreover, in syncope patients with left ventricular dysfunction, inducible ventricular tachycardia was frequent in the presence of CAD and associated with a bad prognosis (7). Therefore, by diagnosing stable CAD and providing additional treatment with vascular protective medication, the prognosis of cardiac syncope patients could be positively influenced. HMG-CoA reductase inhibitors (statins) have become a cornerstone in the treatment of patients with stable CAD due to their lipid-lowering characteristics and additional atherosclerotic plaque stabilization, systemic inflammation and thrombogenicity reducing effects (25). In line with these findings, recent review articles summarize that statins even reduce the incidence of ventricular tachycardia/fibrillation and sudden cardiac death in patients with CAD by their anti-ischemic and possibly also by their antiarrhythmic or anti-inflammatory effects (26, 27).

Study limitations

This study has several limitations that should be mentioned. First, it concerns a study with a relatively small sample size. Secondly, there was some degree of referral bias considering that our institution concerns a tertiary center for patients with syncope. This is confirmed by the fact that within our syncope study population, a higher relative prevalence of cardiac syncope was observed in comparison to previous reports (2, 3). Thirdly, the syncope patients were included if they were referred for CCTA, inducing

some degree of selection bias. The combination of referral as well as selection bias could have contributed to the high prevalence and extent of CAD within the cardiac syncope patients. Also important is the fact that no direct causal relationships could be identified regarding the presence and extent of CAD and syncope due to the present study design, as this would require a prospective interventional study.

CONCLUSIONS

Patients with cardiac syncope show a high presence and extent of CCTA defined CAD in contrast to patients with non-cardiac syncope. These results suggest that CAD may play an important role in the occurrence of cardiac syncope and should be considered in the diagnostic workup and treatment of syncope patients.

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Supplementary
FILES

Supplemental table 1.

Detailed characteristics of syncope patients

Patient characteristics	**Total** ***n=142***	**Cardiac syncope** ***n=49***	**Non-cardiac syncope** ***n=93***	**P-value**
Medication use				
Antihypertensive agent	53 (37)	24 (49)	29 (31)	**0.045**
Statin	29 (20)	12 (25)	17 (18)	0.390
ACEi/ARB	27 (19)	14 (29)	13 (14)	**0.044**
Beta blocker	29 (20)	11 (22)	18 (19)	0.667
Calcium channel blocker	11 (8)	5 (10)	6 (7)	0.513
Diuretic	14 (10)	5 (10)	9 (10)	>0.999
Antiplatelet	21 (15)	13 (27)	8 (9)	**0.006**
Antiarrhytmic agent	4 (3)	3 (6)	1 (1)	0.119
Electrocardiography				
Heartrate, *bpm*	72 (62 – 82)	73 (60 – 85)	71 (63 – 79)	0.610
P-wave duration, *msec*	80 (80-80)	80 (80 - 80)	80 (70 – 80)	0.216
PQ-interval duration, *msec*	156 ± 23	158 ±24	154 ± 22	0.326
QRS-duration, *msec*	92 (84 – 102)	90 (82 – 100)	92 (84 – 104)	0.639
QTc-duration, *msec*	423 (405 – 445)	426 (416 – 452)	417 (400 – 439)	**0.016**
Echocardiography				
LVEF, *%*	60 ± 6	60 ± 8	59 ± 6	0.821
LA volume, *ml*	63 ± 17	64 ± 20	62 ± 16	0.584
LV mass, *mg*	155 ± 37	155 ± 42	155 ± 33	0.969
IVST, *mm*	9 (8 – 9)	9 (8 – 10)	9 (8 – 9)	0.870
PWT, *mm*	8 (8 – 9)	8 (8 – 9)	9 (8 - 9)	0.103
Aortic valve disease				0.061
Sclerosis	16 (13)	7 (16)	9 (11)	
Stenosis	3 (2)	3 (7)	0	
Insufficiency	10 (8)	5 (11)	5 (6)	
Bicuspidy	3 (2)	2 (5)	1 (1)	
Mitral valve disease				0.144
Stenosis	0	0	0	
Insufficiency	6 (5)	4 (9)	2 (2)	

Supplemental table 1. *(continued)*

Patient characteristics	**Total** ***n=142***	**Cardiac syncope** ***n=49***	**Non-cardiac syncope** ***n=93***	**P-value**
Tricuspid valve insufficiency	3 (2)	1 (2)	2 (2)	0.347
Additional testing				
Cardiac stress test	127 (89)	45 (92)	82 (88)	0.578
Holter	121 (85)	42 (86)	79 (85)	>0.999
Electrophysiology study	16 (11)	10 (20)	6 (7)	**0.023**
Implantable Loop Recorder	31 (22)	19 (39)	12 (13)	**0.001**
Cardiac MRI	9 (6)	4 (8)	5 (5)	0.496
Invasive Coronary Angiography	30 (21)	17 (35)	13 (14)	**0.005**
Tilt table test	23 (16)	4 (8)	19 (20)	0.092
Electroencephalography	11 (8)	1 (2)	10 (11)	0.097
MRI Cerebrum	14 (10)	2 (4)	12 (13)	0.139
24-hour blood pressure measurement	9 (6)	1 (2)	8 (9)	0.164
Duplex Carotid Arteries	4 (3)	1 (2)	3 (3)	>0.999

Values are presented as mean (SD standard deviation), median (interquartile range) or as absolute numbers (%). ACEi angiotensin-converting enzyme inhibitor, ARB angiotensin-receptor blocker, CT computed tomography, LVEF left ventricular ejection fraction, LA left atrium, LV left ventricular, IVST interventricular septum thickness, PWT posterior wall thickness, MRI magnetic resonance imaging
Note: *statistically significant parameters are shown as a bold value.*

Chapter

BMI is not independently associated with coronary artery calcification in a large single-center CT cohort

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Abstract

OBJECTIVE

Obesity is associated with cardiovascular disease (CVD) and CVD mortality. However, previous reports showed a paradoxical protective effect in patients with known CVD referred as "obesity paradox". Therefore, the aim of the present study was to investigate the association of body mass index (BMI) with coronary artery calcification (CAC) in a large outpatient cardiac CT cohort.

METHODS

4.079 patients who underwent cardiac CT between December 2007–May 2014 were analysed. BMI and clinical risk factors (current smoking, diabetes mellitus type 2, family history, systolic blood pressure, lipid spectrum) were assessed. Missing values were imputed using multiple imputation. CAC extent was categorized as absent (0), mild (>0-100), moderate (>100-400) and severe (>400).

RESULTS

Multivariable multinomial logistic regression analysis, including all risk factors as independent variables, showed no association between BMI and CAC. Using absence of calcification as reference category, the odds ratios per unit increase in BMI were 1.01 for mild; 1.02 for moderate; and 1.00 for severe CAC (p-values ≥0.103).

CONCLUSIONS

No statistically significant association was observed between BMI and CAC after adjustment for other risk factors.

INTRODUCTION

Obesity is recognized as a well-established risk factor for cardiovascular disease (CVD) and concerns an increasing problem of the public health worldwide. According to the National, Heart, Lung, and Blood Institute criteria, obesity is defined as a body mass index (BMI) equal or greater than 30kg/m^2 which concerns the most widely accepted and used obesity index (1). The European Society of Cardiology guidelines on the prevention of CVD lists obesity as a modifiable cardiovascular risk factor (2). Despite the clear associations between obesity and cardiovascular mortality, it is a matter of debate whether obesity is actually an independent risk factor, since obesity is strongly associated with insulin resistance, type 2 diabetes mellitus, inflammation, dyslipidaemia and hypertension, known as metabolic syndrome (3, 4, 5, 6). There is even a subset of persons with obesity which are considered as "metabolically healthy" due to the fact that these patients have optimal regulated risk factors for CVD and whereby no increase of cardiovascular mortality is observed when compared to healthy subjects (7, 8). Additionally, it is indicated that obesity is associated with CAC and cardiovascular risk particularly in young and middle-aged individual's (9, 10). Previous studies on various patients groups with established CVD reported a paradoxical protective effect of obesity which known as the "obesity paradox" (11, 12, 13). In accordance with this phenomenon, the presence and extent of coronary artery disease (CAD) and especially major adverse cardiovascular events have been inversely associated with BMI (14, 15, 16). A series of reports have suggested that a "U-shaped" relationship exists between coronary artery calcification (CAC) and obesity indices including BMI (15, 16, 17). Despite these observations, the majority of previous studies were performed in patients with established CVD, relatively small study populations, subjects with limited age and extreme categories of BMI. In addition, these study populations are not a good reflection of the daily outpatient clinical practice.

The extent of CAC is associated with significant luminal stenosis and concerns a well-established predictor for major adverse cardiac events (18, 19, 20). Therefore, the aim of the present study was to investigate the association between BMI and presence and extent of CAC in a large single-center outpatient coronary CT cohort.

METHODS

Study population

5.738 consecutive patients from the cardiology outpatient clinic with a low-to-intermediate pretest probability for obstructive CAD, referred for cardiac CT in the period between December 2007 and May 2014 as part of their diagnostic work-up, were selected.

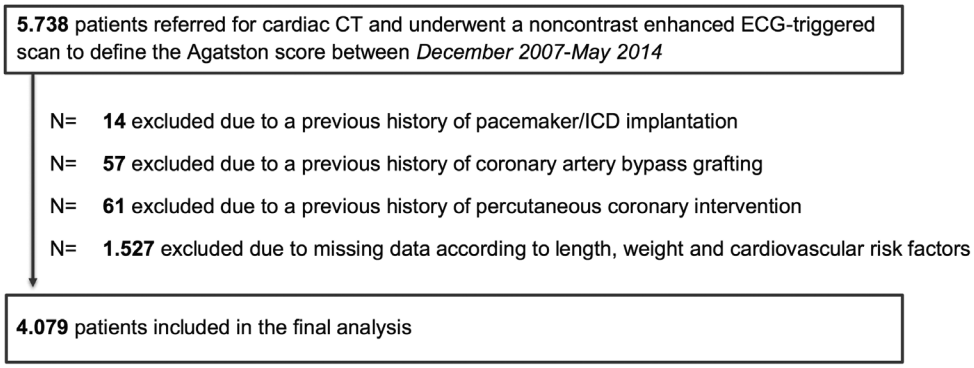
Included were patients who underwent a non-contrast enhanced CT scan to determine the Agatston score (AS) (21). Excluded from the analysis were patients with known history of revascularization (percutaneous coronary intervention (n=61) or coronary

artery bypass grafting (n=57)), unreliable CAC measurement due to a pacemaker or implantable cardioverter-defibrillator (n=14) and missing data on length, weight and classical cardiovascular risk factors (n=1.527). The final analysis was based on 4.079 patients (*Figure 1)*. Missing values according to current smoking (n=229), type 2 diabetes mellitus (n=169), family history (n=315), systolic blood pressure (n=240), total cholesterol (n=676), HDL cholesterol (n=790) and LDL (n=803) were imputed using multiple imputation. Complete data were available for 2857 patients (70%).

This study was approved by the Institutional Review Board (IRB) and Ethics Committee of Maastricht University Medical Center (METC 15-4-119). Written informed consent was waived because data were retrospectively analysed anonymously in accordance with the IRB guidelines. This study complies with the ethical principles of the Declaration of Helsinki.

FIGURE 1.

Flowchart of the study design.



CAC Assessment

A non-contrast gated ECG triggered scan was performed to determine CAC using the Agatston method (21). An attenuation threshold of 130 Hounsfield units (HU) was used to identify calcifications in the main coronary branches. All individual calcifications were manually picked, summed and expressed as the AS. The AS was independently measured by an experienced radiologist and cardiologist. In case of disagreement, consensus was reached by reviewing the findings jointly.

From December 2007 until June 2010, a 64-slice multi-detector CT-scanner (Brilliance 64; Philips Healthcare, Best, The Netherlands; n=1.735) was used to measure CAC. Data acquisition parameters were a slice collimation of 64 x 0.625 mm, a gantry rotation time of 420ms, scan time of 0.4 seconds, tube voltage of 120kV and slice thickness of 3 mm. CAC was measured using dedicated calcium scoring software (Heartbeat-CS, EBW, Philips Healthcare, Best, The Netherlands).

From June 2010 onward, a second generation dual-source CT-scanner was used (Somatom Definition Flash, Siemens Medical Solutions, Forchheim, Germany; n=2.344) to

measure CAC. Data acquisition parameters were: pitch 3.4, slice collimation 2 x 128 x 0.6 mm, gantry rotation time 280ms, tube voltage 120kV, tube current 100-150 reference mAs and slice thickness of 3 mm; reconstruction was performed with a B35f kernel. CAC was calculated using dedicated software (Syngo.Via Calcium scoring, Siemens Healthcare, Forchheim, Germany).

The presence and extent of CAC was categorized as absent (Agatston score=0), mild (Agatston score >0-100), moderate (Agatston score >100-400) and severe (Agatston score >400).

BMI

BMI was divided into clinically relevant categories on the basis of National Heart, Lung and Blood Institute criteria (1): underweight (BMI <18.5kg/m^2), normal weight (BMI 18.5 -24.9 kg/m^2), overweight (BMI 25.0 – 29.9 kg/m^2), class I obesity (BMI 30.0 – 34.9 kg/m^2), class II obesity (BMI 35.0 – 39.9 kg/m^2), and class III extreme obesity (BMI ≥ 40.0 kg/m^2). Additionally, patients with class I, II and III obesity, were combined into one category as having obesity.

Cardiovascular Risk factors

Cardiovascular risk factors were collected prior to cardiac CT. Diabetes mellitus type 2 was defined as fasting glucose levels of ≥ 7mmol/L or treatment with either diet intervention, oral glucose lowering agent or insulin; smoking was defined as current smoking. A positive family history was defined as having a first-degree relative with a history of myocardial infarction or sudden cardiac death before the age of sixty. The systolic blood pressure, total cholesterol, HDL and LDL cholesterol were assessed at the outpatient cardiology clinic prior to cardiac CT.

Missing values according to the cardiovascular risk factors were imputed using multiple imputation.

Statistical analysis

The distribution of continuous variables were described by means and standard deviation (in case of normal distributions) and as median with interquartile range (IQR) (in case of skewed distributions). Differences between CAC categories with respect to continuous variables were tested for statistical significance using one-way analysis of variance (ANOVA) test since all continuous variables were normally distributed. Differences in categorical variables were tested with the Chi-square test.

Multinomial logistic regression analysis was conducted with four CAC categories as dependent variable: absent (AS=0), mild (AS >0-100), moderate (AS >100-400) and severe CAC (AS>400). Absence of calcification (AS=0) was used as the reference category. To evaluate the association between BMI and CAC extent, both univariate and multivariable regression analyses were performed. The multivariate model included BMI, and conventional risk factors for CVD such as age, male gender, diabetes mellitus

type 2, active smoking, systolic blood pressure, total cholesterol, LDL and HDL cholesterol. The multinomial logistic regression analysis provides odds ratios with 95% confidence intervals for each independent variable for three comparisons: mild CAC versus no CAC, moderate CAC versus no CAC and severe CAC versus no CAC. Data were analysed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Only two-sided p-values were used and a p-value ≤0.05 was considered statistically significant.

RESULTS

Study population

The mean age of the total study population was 56 ± 11 years and mean BMI was 27.0 ± 4.7 kg/m^2. 52% of the population were male; 23% were current smokers and 8% had diabetes mellitus type 2. Mean systolic blood pressure was 144 ± 21 mmHg. A total of 1.809 patients (44%) had an AS of zero (no CAC); 1.171 (29%) had an AS between 0 and 100 (mild CAC); 580 (14%) had an AS between 100 and 400 (moderate CAC) and 519 (13%) had an AS >400 (severe CAC). Between the CAC categories there were significant differences with respect to age, male gender, diabetes mellitus type 2, systolic blood pressure, total cholesterol, LDL and HDL (all p-values <0.001). Mean BMI values were similar across the different CAC groups (p-value = 0.083). The baseline characteristics of the total study population according the CAC categories are further described in *Table 1.*

Table 1.

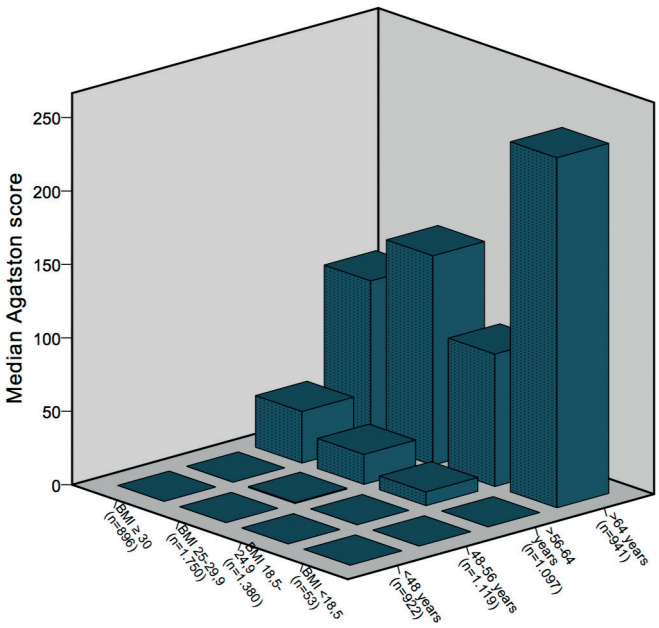
Baseline characteristics of the study population according to the presence and extent of CAC.

	Total ***n=4.079***	**No CAC** ***AS=0 n=1.809***	**Mild CAC** ***AS >0-100 n=1.171***	**Moderate CAC** ***AS>100-400 n=580***	**Severe CAC** ***AS>400 n=519***	**P-value**
Age, *years*	56 ± 11	51 ± 11	58 ± 10	62 ± 9	65 ± 9	<0.001
Male gender, *%*	2.109 (52)	767 (42)	631 (54)	348 (60)	363 (70)	<0.001
BMI, *kg/m^2*	27.0 ± 4.7	26.8 ± 4.9	27.1 ± 4.4	27.4 ± 4.7	27.1 ± 4.6	0.083
Current smoking, *%*	932 (23)	412 (23)	274 (23)	126 (22)	120 (23)	0.865
Diabetes Mellitus, *%*	340 (8)	94 (2)	103 (9)	68 (12)	75 (15)	<0.001
Positive family history, *%*	1.462 (36)	654 (36)	425 (36)	200 (34)	183 (35)	0.812
Systolic blood pressure, *mmHg*	144 ± 21	141 ± 19	145 ± 21	148 ± 21	149 ± 22	<0.001
Total cholesterol, *mmol/L*	5.5 ± 1.2	5.5 ± 1.1	5.5 ± 1.2	5.5 ± 1.2	5.1 ± 1.2	<0.001
LDL cholesterol, *mmol/L*	3.4 ± 1.1	3.4 ± 1.0	3.5 ± 1.1	3.4 ± 1.1	3.1 ± 1.1	<0.001
HDL cholesterol, *mmol/L*	1.4 ± 0.4	1.4 ± 0.5	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	<0.001

AS: Agatston score; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

FIGURE 2.

Median Agatston score according to BMI and age categories.



Association of BMI with CAC

Figure 2 visualizes the relationship of median AS with BMI within quartiles of age. Below the age of 56 years, the median AS is zero within all BMI categories. Within the age category >56-64 years, there is a trend towards higher median AS with increasing BMI. Median AS is highest in the BMI category <18.5 kg/m^2 years with age >64 years. However, this should be interpreted with caution since this group only contains 10 patients.

Log transformation of the dependent variable AS did not result in a normal distribution due to a large proportion of patients with a zero value for AS. Therefore, a classification into four categories was used to perform multinomial logistic regression analysis. No CAC (AS=0) was used as baseline category and was compared with three alternative categories: mild (AS >0-100), moderate (AS >100-400) and severe CAC (AS >400). Table 2 shows the results from a univariate multinomial logistic regression analysis (without adjustment for other risk factors) and presents the odds ratio per unit increase in BMI with 95% CI for each alternative category when compared with the baseline category (AS=0). BMI showed only a significant positive association in the comparison of moderate CAC with no CAC (OR: 1.02, 95% CI 1.01-1.05, p=0.012). No significant association was observed for BMI when comparing mild CAC with no CAC (OR: 1.01, 95% CI 0.99-1.03, p=0.175) and severe CAC with no CAC (OR: 1.01, 95% CI 0.99-1.03, p=0.328) (*Table 2,* model 1).

Table 2 also displays the results from a multivariable multinomial logistic regression analysis, including BMI, and conventional risk factors for CVD such as age, male gender,

Table 2.

Multinomial logistic regression analysis of factors associated with odds AS.

	Mild CAC *AS >0-100*		**Moderate CAC *AS >100-400***		**Severe CAC *AS >400***	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
AS=0	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Univariate model						
BMI, *kg/m²*	1.01 (0.99-1.03)	0.175	1.02 (1.01-1.05)	**0.012**	1.01 (0.99-1.03)	0.328
Multivariate model						
BMI, *kg/m²*	1.01 (0.98-1.02)	0.952	1.02 (1.00-1.05)	0.103	1.00 (0.97-1.02)	0.774
Age, *years*	1.09 (1.08-1.10)	**<0.001**	1.15 (1.14-1.17)	**<0.001**	1.21 (1.19-1.23)	**<0.001**
Male gender, *yes vs. no*	2.22 (1.85-2.63)	**<0.001**	3.85 (3.03-4.76)	**<0.001**	6.67 (5.00-8.33)	**<0.001**
Diabetes mellitus, *yes vs. no*	1.69 (1.20-2.38)	**0.002**	2.22 (1.52-3.23)	**<0.001**	2.50 (1.67-3.85)	**<0.001**
Family history, *yes vs. no*	1.20 (1.01-1.43)	**0.040**	1.28 (1.02-1.61)	**0.031**	1.59 (1.23-2.04)	**<0.001**
Current smoking, *yes vs. no*	1.52 (1.25-1.85)	**<0.001**	1.96 (1.49-2.56)	**<0.001**	2.56 (1.92-3.45)	**<0.001**
Systolic blood pressure, *mmol/L*	1.00 (1.00-1.01)	**0.041**	1.01 (1.00-1.02)	**0.001**	1.01 (1.00-1.01)	**0.005**
Total cholesterol, *mmol/L*	1.04 (0.84-1.29)	0.732	0.97 (0.75-1.26)	0.809	0.94 (0.70-1.26)	0.670
LDL cholesterol, *mmol/L*	0.99 (0.79-1.24)	0.908	1.05 (0.79-1.34)	0.764	0.88 (0.64-1.22)	0.443
HDL cholesterol, *mmol/L*	0.81 (0.64-1.04)	0.097	0.91 (0.66-1.24)	0.534	0.63 (0.43-0.92)	**0.018**

diabetes mellitus type 2, active smoking, systolic blood pressure, total cholesterol, LDL and HDL cholesterol. BMI did not independently predict the extent of CAC: mild (OR: 1.01, 95% CI 0.98-1.02, p=0.952, moderate (OR: 1.02, 95% CI 1.00-1.05, p=0.103), and severe (OR: 1.00, 95% CI 0.97-1.02, p=0.774) (*Table 2*, model 2).

The classical risk factors: age, male gender, diabetes mellitus type 2, family history, current smoking and systolic blood pressure independently predicted CAC (all p-values ≤0.041) showing increasing odds ratios across CAC extent.

DISCUSSION

Within the present study, the association between BMI and CAC was investigated in a large single-center outpatient coronary CT cohort. The main finding of this study was that no significant independent association was observed between BMI and presence and extent of CAC. Only age, male gender and classical cardiovascular risk factors, including diabetes mellitus type 2, family history, current smoking and systolic blood pressure showed an independent positive association with the extent of CAC. Based upon the findings of the present study, it might be reconsidered whether a high BMI should serve as an independent risk factor for coronary atherosclerosis in patients without known established CVD.

Previously, several studies have evaluated the association between body morphology and CAC. Allison et al studied a healthy population with a mean age of 57 and BMI of 27kg/m^2 where they described higher BMI as a significant predictor of CAC (22). Comparable findings were reported in the Multi-Ethnic study of Atherosclerosis (MESA) and the CARDIA study after adjustment for risk factors (6, 10, 23). The Dallas Heart study also evaluated the association between obesity and prevalent atherosclerosis within a large population-based study. They observed weak, although positive associations between BMI and prevalent CAC in contrast to strong associations for waist-to-hip ratio (WHR) and prevalent CAC (24). Fujiyoshi et al also demonstrated a significant positive association of BMI and CAC within a multi-ethnic study cohort independent of classical risk factors (9). However, their study population existed of unselected male subjects with a relatively young age (40-49). A significant positive association between BMI and CAC was not observed in this study. A possible explanation for the lack of significant findings is the use of multinomial logistic regression analysis with AS classified into four categories as dependent variable, whereas other studies used binary logistic regression with presence or absence of CAC as dependent variable (9, 10, 23).

Comparison of several categories according to extent of CAC with a reference category without any calcification has the advantage that the strength of the association with risk factors can be evaluated according to extent of CAC. However, the sample size per category is smaller and thereby the power to detect weak or moderate associations decreases. Since the AS is a non-normally distributed variable due to a large amount of zero variables, where log transformation cannot correct for, the possibilities for additional statistical analysis are limited.

There is also a subset of persons with obesity which are considered as "metabolically healthy" due to the fact that these patients have optimally regulated risk factors for CVD and whereby no increase of CV mortality is observed when compared to healthy subjects (7). Since metabolically healthy obese individuals represent 10%–45% of the adult obese population, one could state that the persons with obesity within the present study population are especially patients with "metabolically healthy" obesity since cardiac CT is recommended as an alternative to stress imaging techniques in stable chest pain patients with a low to intermediate pre-test probability for obstructive CAD (8, 25).

Recent studies have described an "obesity paradox" indicating that after CVD has been diagnosed, mildly obese and persons with obesity have a similar or even decreased mortality risk compared to patients with normal weight (15, 16). This U-shaped association has also been observed for body size and CAD. In 2012, Kovacic et al studied a large group of patients who underwent percutaneous coronary intervention and identified an inverse correlation between BMI and index lesion calcification (15). Dangas et al also reported the inverse relationship between body size and CAC in patients with obstructive CAD (16). With regard to the previous studies that observed a U-shaped association of BMI with mortality as well as with CAD, no clear underlying pathophysiological mechanisms have been established which could explain this possible complex relationship. Interesting is the fact that besides the "obesity paradox" there are also reports of a "calcification paradox", whereby reduced bone mineral density is associated with increased vascular calcification. It is predicted that persons with increased BMI have less osteoporosis and an inverse relationship between BMI and CAC may apply (20, 26, 27). Within the present, which particularly included subjects without a known history of obstructive CAD, no protective effect of high BMI was observed. It could be assumed that this explains the controversial finding, since the previous studies reporting an inverse association between body size and CAC are particularly performed in patients with known CVD or obstructive CAD. Kim et al have discussed that one must be careful when interpreting the "obesity paradox" because of the fact that this phenomenon has been investigated in cohorts with established CVD where there is a difference in risk factors for recurrent coronary heart disease in normal weight or underweight patients in contrast to persons with obesity (28). Selection of subjects in whom the disease is already present or has previously occurred can result in so-called "index event bias" explaining paradoxical findings in medical research. Namely, due to conditioning on the disease or event, dependency between risk factors occurs despite these risk factors are independently associated within the general population (29, 30).

Within the present study cohort of patients with a low-to-intermediate risk for obstructive CAD, no significant association was observed between BMI and CAC in contrast to age, male gender, diabetes mellitus type 2, family history, current smoking and systolic blood pressure. This could influence daily clinical practice, since it has to be reconsidered whether a high BMI should serve as an independent risk factor for coronary atherosclerosis in patients without known established CVD and low-to-intermediate risk for obstructive CAD.

The present study has some limitations that have to be mentioned. Firstly, the patient samples in the lowest and highest BMI categories were small compared to the other groups and therefore could lack statistical power. It is reasonable that especially in case of a very high BMI the physician might avoid a CT-scan as diagnostic tool, because of the effects of obesity on image quality. However, this study reflects a cardiology outpatient clinic population since we included a large representative sample from a single-center outpatient CT cohort. Secondly, only BMI was available within the present study population, whereby one could argue that BMI lacks discriminatory power to differentiate between body fat, metabolic state of this body fat and lean mass and thus to diagnose obesity. However, BMI is the most widely accepted obesity index and still used by the World Health Organization to define obesity. The European Society of Cardiology guidelines on CVD prevention also recommend BMI as the obesity index to predict CVD risk in routine practice (2).

CONCLUSION

Within the present study, no significant association was observed between BMI and CAC after adjustment for other risk factors. Therefore, it needs to be reconsidered whether a high BMI should concern as an independent risk factor for presence and extent of CAC in outpatient low-to-intermediate risk patients.

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Chapter

GENERAL DISCUSSION AND SUMMARY

GENERAL DISCUSSION AND SUMMARY

Both serum biomarkers and cardiac computed tomography (CT) analysis have the ability to reveal biological processes underlying coronary artery disease (CAD). This thesis investigated the relationship between CAD as defined by cardiac CT and serum biomarkers, to study its diagnostic and risk stratifying capabilities. In addition, the role of cardiac CT within the diagnostic work-up for suspected stable CAD was investigated in different patient populations.

CORONARY CT ANGIOGRAPHY AND BIOMARKERS

Since the clinical introduction of hs-cTn assays, more accurate detection of low but elevated levels of circulating cardiac troponins became feasible (1). Low serum levels of hs-cTnT have been previously associated to the presence and extent of CAD as well as vulnerable plaque phenotypes and thus could serve to identify patients at risk for an acute cardiovascular event (2, 3). However, the transfer to more sensitive assays was accompanied by a decline in specificity, as circulating hs-cTn levels are elevated in many other conditions, for example in patients with renal dysfunction (4).

In ***chapter 2*** of this thesis we provided (for the first time) insights into the interpretation of hs-cTn concentrations in patients with stable chest discomfort, identifying not only imaging parameters but also renal function as independent and strong contributors to circulating hs-cTn concentrations. Additionally, we found that serum hs-cTnT as well as hs-cTnI were significant prognostic markers for adverse events, independent from established risk predictors, such as coronary calcium score. These results therefore indicate that both hs-cTn's are not only useful risk stratifyers in patients at serious risk for adverse events (5-8), but also contribute significantly to risk stratification in a low-risk stable CAD population underlining their comprehensive capability to define the patient at risk.

In addition, coronary CT angiography (CCTA) is capable of defining high-risk plaques features associated with the occurrence of acute coronary syndrome (ACS). Prognostic plaque characteristics that have been described are especially presence of non-calcified plaques, spotty calcification, outward remodeling and total plaque volume (9). Versteylen et al. previously showed that semi-automated plaque quantification identified several parameters predictive for ACS and provided incremental prognostic value over clinical risk profile and conventional cardiac CT reading (10). In ***chapter 3***, we went a step further and investigated the association of the cardiospecific biomarkers, hs-cTnT and NT-proBNP with coronary atherosclerotic plaque characteristics using dedicated software in a hypothesis-generating setting. Our data indicate that hs-cTnT and NT-proBNP concentrations showed significant associations with total plaque volume, calcified volume,

plaque burden, remodeling index and number of plaques. Furthermore, we investigated the association of the *segment involvement score* with hs-cTnT, NT-proBNP and outcome, showing significant associations between this scoring system and these biomarkers.

Our findings support the use of a comprehensive coronary risk scoring system, which incorporates novel coronary plaque quantification parameters and conventional cardiac CT parameters combined with the use of serum biomarkers.

Consequently, coronary plaque parameters could reflect total vulnerable plaque material whereas cardiospecific biomarkers reflect disease activity. Such an approach could define vulnerability of the entire patient rather than of a single plaque and thus could have an impact in future risk stratification of patients with stable chest pain.

Table 1.

Characteristics of detailed plaque parameters versus cardiospecific biomarkers in defining the vulnerable patient.

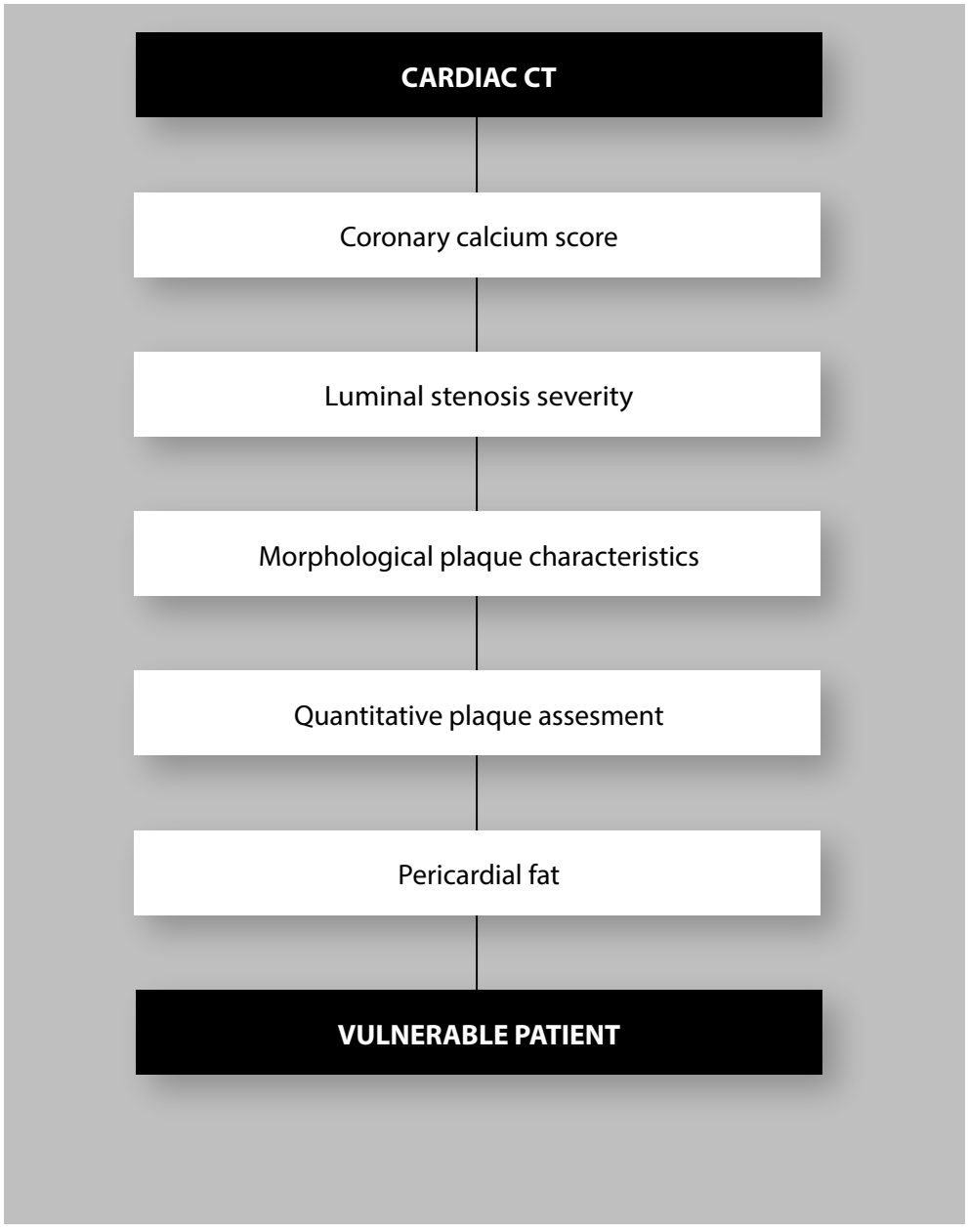
Plaque parameters	Cardiospecific biomarkers
Presence and extent of disease	Disease activity
High-risk plaque phenotyping	Dynamicity
Plaque instability	Systemic vulnerability
Prognostic implications	Prognostic implications

As described in ***chapter 3***, using dedicated post-processing software, detailed volumetric plaque parameters can be defined in addition to conventional cardiac CT reading in order to improve risk stratification in stable chest pain patients. Besides plaque parameters, cardiac CT is also able to define pericardial fat volume which already has been extensively correlated to CAD and the occurrence of cardiovascular events. In contrast, little is known on the role of CT in patients with diastolic heart failure which concerns a major cause of morbidity and mortality, and its pathological mechanisms remain poorly understood. We therefore studied (***chapter 4***) the correlation between pericardial fat (PF) using semi-automated dedicated software and diastolic function within a middle-aged, low-risk population with normal systolic and diastolic left ventricular function as defined on cardiac ultrasound. A correction for metabolic risk factors was performed in order to evaluate these relationships independently. Within linear regression analyses, we showed that PF was significantly associated with the following diastolic function parameters on ultrasound: LAVI, e' lateral, e' septal, E/e', and TR when corrected for age, BMI, and sex. These associations indicate that even within a healthy population with a potentially normal diastolic function PF is independently associated with diastolic function parameters. A potential underlying mechanism of this may be that increased PF may have mechanical or biological properties, that can impare diastolic function.

This study adds to the growing body of knowledge on possible mechanisms in the development of diastolic failure. Based upon the results of this study, we confirm that PF, even in healthy subjects with normal cardiac function and without diabetes, affects diastolic function. The causality of this effect and the relationship with fibrosis remains to be determined further.

FIGURE 1.

Defining the vulnerable patient using cardiac CT.



CARDIAC CT WITHIN THE DIAGNOSTIC WORK-UP FOR SUSPECTED STABLE CAD

Despite the wide use of cardiac CT in patients presenting with stable chest pain, currently there are no recommendations for CAD within the routine diagnostic workup of patients presenting with syncope (11). Nevertheless, diagnosing CAD within syncope patients in an early stage could have important mechanistic, prognostic and therapeutic clinical implications. In ***chapter 5***, we therefore investigated the presence and extent of CAD, as defined by CCTA, in patients presenting with syncope at the outpatient cardiology clinic. We showed that cardiac syncope patients had a higher presence and extent of CAD in comparison with non-cardiac syncope patients. In addition, all other coronary CT parameters like coronary calcium score, segment involvement score and stenosis score were also significantly higher in cardiac syncope patients compared to non-cardiac syncope patients. When compared to stable chest pain controls, patients with cardiac syncope showed a higher, however, non-significant, prevalence of any CAD (72% versus 63% respectively) and percentage of severe luminal stenosis (33% versus 19%).

The relationship between CAD and subsequently cardiac ischemia causing syncope could be multiple, including induction of nonsustained ventricular arrhythmias and sinoatrial or atrioventricular block. Apart from a direct relationship, indirect mechanisms may be important, including old myocardial infarction with ventricular remodeling as a basis for reentrant or adrenergic ventricular tachycardia; likewise, atrial remodeling leading to late onset atrioventricular nodal tachycardia or atrial tachycardias may at times occur with well-known hemodynamic compromise eliciting syncope at the beginning of the tachycardia. In these circumstances, CAD may be causal or contributory for syncope whereby one could state that interventional and vascular prophylactic management may help to reduce further syncope in these patients, for example calcium channel blockers and (long-acting) nitrates. In all other cases, CAD should be considered as coincidental wherefore vascular prophylactic vascular management may not be indicated in the management of syncope. Taken together, these results suggest that the non-invasive evaluation of CAD, using CCTA should be considered within the diagnostic workup of patients presenting with cardiac syncope at the outpatient cardiology clinic. Additionally, CCTA may also show alternative causes for cardiovascular syncope such as congenital anomalies of coronary arteries, hypertrophic cardiomyopathy, pulmonary embolism, obstructive valvular disease, intracardiac masses and pericardial diseases.

Obesity concerns an increasing problem of the public health worldwide and is listed as a modifiable cardiovascular risk factor within *the European Society of Cardiology guidelines on the prevention of CVD* wherein body mass index (BMI) is the recommended obesity index (12). In ***chapter 6*** of this thesis, we investigated the association between BMI and presence and extent of coronary artery calcification (CAC) in a large single-center outpatient coronary CT cohort including 4.079 patients. We used CAC as an outcome variable since the extent of CAC is associated with significant luminal stenosis and concerns a well-established predictor for major adverse cardiac events (13-15). Within this study, Interestingly, we could not observe a relation between BMI and CAC without and even after adjustment for other

traditional cardiovascular risk factors and postulated that in outpatient low-to-intermediate risk patients, obesity should not be considered as an independent risk factor for the presence and extent of CAC. The fact that we could not observe a positive association between BMI and CAC could be explained by the observation that there is a group of "metabolically healthy" obese patients which account for up to 10%-45% of the obese patients (16). Since our study was performed within a large coronary CT-cohort which represents a low-to-intermediate risk population we could speculate that the obese patients included in our study are especially patients without the metabolic syndrome (17). One could also argue that BMI lacks discriminatory power to differentiate between body fat, metabolic state of this body fat and lean mass and thus to correctly diagnose obesity. However, BMI is widely accepted and still used by the World Health Organization to define obesity and is used to predict CVD risk in routine practice according to *the European Society of Cardiology guidelines on CVD prevention* (12).

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Chapter

SCIENTIFIC IMPACT

SCIENTIFIC IMPACT

Over the last decade, cardiac computed tomography (CT) has developed as a highly accurate non-invasive anatomical diagnostic imaging modality. Currently, ESC guidelines describe a central role for cardiac CT in diagnosing coronary artery disease (CAD). Increasing experience and technological advances ensure ever improving image quality with relatively low radiation exposure due to individualized acquisition. The role and the accuracy is dependent on the pre-test probability wherefore it is widely used in patients with a low to intermediate suspicion of obstructive CAD.

In addition to its widespread use in patients with chest pain, other patient populations may also benefit from early detection of CAD. We presented for the first time, that using cardiac CT in patients with suspected cardiac syncope could be of utmost interest since this could have important mechanistic, prognostic and therapeutic clinical implications. We believe that these data will serve as a good basis for future research into vascular mechanisms of syncope or the cost-effectiveness of cardiac CT in patients presenting with syncope.

Conventional cardiac CT-reading reports only coronary calcium score and presence of atherosclerosis and coronary stenosis caused by CAD. The data in this thesis show that cardiac CT can be used to quantify cardiovascular disease beyond mere coronary stenosis grading. These novel imaging hallmarks of CV disease can be quantified using specialized software, and in turn can be used as a risk stratifying imaging biomarker. In chapter 3 of this thesis we used dedicated software, defining detailed volumetric plaque parameters and investigated their association with cardiospecific biomarkers. These data support the clinical applicability of a multibiomarker approach combining these novel sophisticated CT-angiographic parameters with established cardiospecific serum biomarkers. We foresee that this combined approach will improve prediction of atherosclerotic plaque progression. Furthermore, the present data represent a firm stepping stone for future studies using sequential analysis of atherosclerotic plaques using advanced cardiac CT imaging e.g. to elucidate pathophysiology of plaque progression and the impact of novel interventional therapies including lipid-lowering, interleukin inhibition and novel anticoagulants. Such studies are currently underway, and plaque analysis has been established as a surrogate imaging endpoint. This allows rapid evaluation of novel therapies, and hopefully more rapid introduction of promising novel agents. Future research should focus more on individualized risk assessment and treatment of CAD, and include features such as advanced plaque analysis and epicardial adipose tissue. This should help guide treatment. Ultimately combining both biomarker, genetic and imaging data will enable more personalized risk assessment and preventive targeted treatment.

Chapter

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Nederlandse samenvatting

Hart- en vaatziekten blijven de hoofdoorzaak van overlijden in de Westerse wereld. Zo overlijdt 1 op de 5 mensen in Nederland hieraan. De belangrijkste oorzaak is kransslagaderlijden en de gevolgen daarvan, welke ontstaat door atherosclerose of aderverkalking wat een multifactorieel chronisch inflammatoir proces betreft. De verstoring van een atherosclerotische plaque in de kransslagaderen en de daaropvolgende afsluiting middels een bloedklonter zijn de pathologische kenmerken van een acuut hartinfarct, dat kan leiden tot overlijden. Ondanks alle ontwikkelingen in de diagnostiek en spectrum aan verschillende beeldvormingsmodaliteiten blijft het een uitdaging om het risico op hart- en vaatziekten en events op inidividueel niveau goed te bepalen.

Een CT-scan van het hart is een veelbelovende niet-invasieve beeldvormende techniek waarbij vernauwingen van de kransslagaderen op een veilige en snelle manier uitgesloten/onderzocht kunnen worden. Naast het onderzoeken van vernauwingen van de kransslagaderen kan er middels een CT-scan van het hart meer informatie verkregen worden middels aanvullende analyses die van belang kunnen zijn voor de risicostratificatie van een individuele patiënt. Zo zijn er onder andere specifieke plaquekenmerken die een goede voorspelling kunnen geven voor het optreden van toekomstige events onafhankelijk van de ernst van vernauwing. Ook kan op een eenvoudige wijze het vetvolume rondom het hart bepaald worden middels speciale software welke gerelateerd is aan hart- en vaatziekten alsook events.

Daarnaast zijn er ook verschillende cardiale biomarkers (afvalstoffen) die eenvoudig in het bloed gemeten kunnen worden. Voor de diagnostiek rondom een acuut myocardinfarct worden hoogsensitieve troponine bepalingen gebruikt vanwege hun zeer hoge nauwkeurigheid ten opzichte van de eerdere varianten. Daarnaast kan deze bloedbepaling ook gebruikt worden als risicostratificatietool bij patiënten met stabiele pijn op de borst. Eerdere onderzoeken hebben namelijk aangetoond dat hoogsensitieve troponineconcentraties (zelfs die onder de diagnostische afkapwaarde voor een acuut myocardinfarct) geassocieerd zijn met een verhoogd risico op cardiovasculaire events. Echter, door het ontwikkelen van deze hoogsensitieve cardiale troponine zijn er meer patiënten waarbij deze biomarkers in het bloed worden gedetecteerd. Dit beïnvloedt de positief voorspellende waarde van deze test. Zo vertonen patiënten met een verminderde nierfunctie ook verhoogde troponinewaardes in het bloed.

In ***hoofdstuk 2*** van dit proefschrift is derhalve onderzocht in welke mate de nierfunctie bijdraagt tot hogere hoogsensitieve cardiale troponine concentraties bij patiënten met stabiel pijn op de borst. In dit groot onderzoek cohort van 1.864 patiënten, die poliklinisch werden doorverwezen voor een CT-scan van de kransslagaderen, werden gedetecteerde troponinewaardes toegeschreven aan de aanwezigheid en ernst van coronairlijden. Opvallend was dat in dit onderzoek werd aangetoond dat de associatie met de nierfunctie onafhankelijk en zelfs sterker was dan de associatie met cardiale parameters voor de aanwezigheid en uitgebreidheid van coronairlijden.

In ***hoofdstuk 3*** van dit proefschrift werd de relatie tussen cardiale (bloed) biomarkers (afvalstoffen) en hoog risico atherosclerotische plaquekenmerken op cardiale CT onderzocht

middels het gebruik van additionele software. Dit onderzoek toonde een duidelijk verband tussen deze biomarkers en hoogrisico volumetrische plaquebepalingen zoals totale plaque volume. Deze hoogrisico plaquebepalingen reflecteren namelijk de totale hoeveelheid van vulnerabele atherosclerotische plaques, terwijl de cardiale biomarkers de ziekteactiviteit weergeven. Dit onderzoek ondersteunt derhalve het concept dat het combineren van hoogrisico plaquekenmerken/bepalingen met biomarkers de risicostratificatie van patiënten met stabiele pijn op de borst verder kan optimaliseren.

Hoofdstuk 4 betreft een analyse van een onderzoekspopulatie van 254 gezonde patiënten waarbij de relatie tussen vet rondom het hart en diastolische parameters op het echocardiogram werden onderzocht. De resultaten van dit onderzoek lieten zien dat het vet rondom het hart geassocieerd is met vier belangrijke diastolische (=relaxatie) parameters bepaald middels echocardiogram, onafhankelijk van leeftijd, body mass index (BMI) en geslacht. Een verhoogde hoeveelheid vet rondom het hart zou namelijk mechanisch kunnen bijdragen aan diastolische functie door enige compressie/weerstand en anderzijds door lokale inflammatoire effecten middels het induceren van fibrose. Hoewel er geen precieze causaliteit is onderzocht draagt dit onderzoek bij aan het achterhalen van mogelijke mechanismen die kunnen bijdragen aan het ontstaan van diastolisch hartfalen.

In ***hoofdstuk 5*** van dit proefschrift werd de ernst en uitgebreidheid van kransslagaderlijden onderzocht in patiënten die zich op de polikliniek cardiologie presenteerden met (een) wegraking(en). Dit onderzoek werd verricht omdat er zeer beperkte data is omtrent het voorkomen van coronairlijden in deze patiëntenpopulatie en er derhalve geen standaard aanbevelingen zijn hiertoe. De onderzoekspopulatie bestond uit patiënten met een cardiale wegraking en patiënten met een niet-cardiale wegraking: het onderscheid werd gemaakt op basis van een zeer uitgebreide anamnese en aanvullende diagnostiek. Middels dit onderzoek werd aangetoond dat patiënten met een cardiale wegraking een hogere prevalentie van (ernstig) coronairlijden hebben in tegenstelling tot patiënten met een niet-cardiale wegraking. Deze resultaten suggereren dat het uitsluiten van kransslagaderlijden overwogen dient te worden bij patiënten die zich voornamelijk presenteren met een cardiale wegraking.

Overgewicht wordt erkend als een risicofactor voor hart- en vaatziekten en vormt wereldwijd een toenemend probleem voor de wereldgezondheid. Ondanks de duidelijke associaties tussen overgewicht en cardiovasculaire mortaliteit blijft het een discussiepunt of overgewicht een onafhankelijke risicofactor is aangezien de sterke associatie met de andere klassieke cardiovasculaire risicofactoren zoals diabetes mellitus type 2, hypertensie en hypercholesterolemie. In ***hoofdstuk 6*** van dit proefschrift onderzochten we derhalve de associatie tussen BMI en de aanwezigheid en ernst van coronaire arteriële calcificatie (CAC) in een poliklinisch CT-cohort met 4.079 patiënten. We gebruikten CAC als uitkomstvariabele aangezien de mate van CAC geassocieerd is met stenose-ernst en een zeer goede voorspeller is voor cardiovasculaire events. Interessant is dat er binnen dit onderzoek geen relatie werd vastgesteld tussen BMI en CAC onafhankelijk van correctie voor traditionele cardiovasculaire risicofactoren.

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About the author

***Sibel Altintas* was born on 18 June 1988 in Maaseik, Belgium**. She attended high school at *het Koninklijk Atheneum* in Maasmechelen where she graduated in 2006. The same year she started her medical training at the faculty of Health and Life Sciences at the Maastricht University, Maastricht, the Netherlands, and obtained her medical degree in July 2012. During her medical training she developed a great interest in Cardiology. Between September 2012 and February 2013 she worked as a physician at the Cardiology department of the Maastricht University Medical Center+, the Netherlands. In 2013, she was offered a position as PhD-candidate in cardiac computed tomography at the deparment of Cardiology and Radiology under supervision of Prof. dr. H.J.G.M. Crijns, Prof. dr. J.E. Wildberger and Dr. B.L.J.H. Kietselaer. During this period, she presented her research at several national and international congresses. The results of this research are presented in this thesis.

In August 2016, she started her clinical Cardiology training under supervision of Dr. E.C. Cheriex and Drs. N.H.T. Dinh. She will finish her training in Cardiology at the end of March 2023. Afterwards she will start a fellowship on advanced cardiovascular imaging and cardiac rehabilitation at the Virga Jesse hospital in Hasselt (Belgium) under supervision of Prof. dr. Dendale. This fellowship will be in behalf of a function as Cardiologist in AZ Vesalius hospital in Tongeren, in order to join the team of Dr. P. Stas and colleagues. She currently lives in Maasmechelen with her husband Mustafa and their son Musa and daughter Berra.

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