Quality of CT in Diagnoses Atherosclerosis

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Abstract: _Introduction: The primary endpoint of this study was to determine Quality of CT in diagnoses atherosclerosis. Secondary endpoints were to evaluate the risk factors and determine the predictors of PVA. Methods: The presence of atherosclerotic disease was assessed using ultrasonographic vascular examination in 20 asymptomatic patients. All patients with presence of stenosis over 55% and moderate-to-severe cardiovascular risk profile underwent CCTA to identify atherosclerotic. Results: Among 20 participants, 5 patients had no evidence of atherosclerotic plaque while 15 patients had atherosclerotic plaque. Of 15 patients with atherosclerotic plaque, 10 patients had single vessel disease, 3 patients had double vessel disease and 2 patients had triple vessel disease; and among these patients, those who also presented with stenosis over 55% underwent CCTA. Coronary stenoses found included normal (6 %), haemodynamically insignificant lesions (30%), significant lesions (25 %) and total artery occlusion (3%). Based on the coronary vessel involved, they were categorised as single coronary disease (41.0%), double coronary disease (42.0%) and triple coronary disease (17.0%). CACS was significantly higher in patients with double vessel disease or triple vessel disease when compared to those with single vessel disease. Conclusion: Our study confirmed not only the high sensitivity of CCTA for highlighting CAD but also its negative predictive value for excluding the presence of coronary stenosis or ischaemia. Good correlation was found between PVA and CACS, and the risk factors for PVA were confirmed._

Keywords: CT calcium score, coronary artery disease, coronary angiography By CT

1. Introduction

Atherosclerosis, a systemic disease that affects the coronary, peripheral and cerebrovascular arteries, is the dominant cause of cardiovascular disease (CVD), including acute myocardial infarction (AMI), chronic heart failure, stroke and claudication, especially in Tabook region It affects primarily the intima in medium-sized and large arteries, resulting in intimal thickening, and may lead to luminal narrowing and inadequate blood supply. (2) Mature atherosclerotic plaque typically consists of two main components, one of which is lipid-rich and soft, and the other is collagen-rich and hard. The flow-limiting potential of an intimal plaque may be modified by reactive changes in the underlying media and adventitia that may attenuate (positive remodelling) or accentuate (negative remodelling) luminal obstruction and the consequent haemodynamic impact of the plaque. (3)

It is widely known hat endothelial dysfunction is the first pathogenic event in the atherosclerotic process. Endothelial dysfunction, in fact, causes changes in vascular homeostasis that make the vessel more vulnerable to dangerous events. On the basis of these considerations, cerebrovascular disease, peripheral arterial disease (PAD) and coronary artery disease (CAD) represent different faces of the same coin that recognises the common denominator in atherosclerosis. This consideration suggests a correlation between CAD and the atherosclerotic involvement of other arterial districts, such as the carotid/aortic/femoral district, called polyvascular atherosclerosis (PVA). The high prevalence of CVD in Western countries could, in fact, be explained just by the large spread of 'pro-atherogenic' lifestyles, such as smoking, sedentary lifestyle and diets too rich in fats. (4) Concomitant CAD and PAD is associated with a two- to threefold increased risk of CVD mortality. (1) Patients with PAD have more severe CAD manifested by higher frequency of left-main and multivessel CAD, (5) a physical function impairment and worse quality of life. (6)

These results were confirmed by Steg et al, (1) who demonstrated that mortality and the risk of future cardiac events increases progressively with the extension of the atherosclerotic process in different parts of the body, stressing that atherosclerosis is a systemic disease.

The Alliance study, (7) conducted on 9,783 patients hospitalised for AMI in France from 2000 to 2005, showed that PVA represents an important predictor of prognosis. This result could be explained by not only the greater severity of the atherosclerotic process but also the prevalent diagnostic and treatment attitudes, which are more conservative for this subset of patients. Many studies have shown that patients with PVA are considered as a risk category and, for this reason, are undertreated. (8)

Early diagnosis of PAD in patients with CAD should prompt aggressive risk factor modification to slow the progression of atherosclerosis, and prevent premature death, heart attack and stroke. The detection of CAD in patients with PVA is important to prevent cardiac mortality and morbidity. Recently, there has been an increased interest in atherosclerosis of the lower extremity arteries and its presence as multifocal disease (carotid/aortic/femoral). However, awareness in the general population and the medical community of non-coronary artery diseases as well as its major prognostic implications remains relatively low. (9)

The primary endpoint of the present study was to determine the prevalence of coronary atherosclerotic lesions and coronary artery calcium score (CACS), detected using coronary computed tomography angiography (CCTA), in patients with PVA. Secondary endpoints were to evaluate the prevalence of cardiovascular risk factors in patients enrolled in the study and determine the predictors of PVA.

2. Methods

This prospective study included 20 asymptomatic patients (age range 40–40 years) undergoing ultrasonographic vascular examination (UVE) at the Intensive Cardiology Care Unit of Deba General Hospital, Tabook KSA, between Sep 2018 and Feb 2019. The patients enrolled in the study were asymptomatic for symptoms and CVD. The age range of 40–70 years was chosen as this is the period when CVDs most often occur in patients.

During the study period, 20 potential asymptomatic participants underwent a routine UVE (carotid investigation of the extracranial carotid arteries [i.e. the common, internal and external carotid arteries], abdominal aorta and femoral district) in order to evaluate for atherosclerotic vascular involvement. Of these patients, 2 were not eligible for inclusion in the study. The most common reasons for ineligibility were: bilateral carotid artery occlusions, recent endovascular interventions, monolateral endoarterectomy), presence of aortic abdominal aneurysm) and peripheral revascularisation

Potential participants were considered to be asymptomatic for PVA (carotid arteries, abdominal aorta and femoral arteries) if they had never experienced a transient ischaemic attack, amaurosis fugax, stroke, abdominal pain or claudication. Patients were excluded from the study if they had symptomatic carotid, abdominal or peripheral artery diseases, current infectious or inflammatory disease, recent operations or endovascular interventions, bilateral carotid or femoral-popliteal occlusion, vascular stent implantation or monolateral/bilateral endoarterectomy.

A patient was categorised as a smoker if he had smoked cigarettes, cigars or a pipe within the past 30 days. Body weight was measured using a balance scale. Body mass index was computed as the ratio of weight to the square of height (kg/m2).

Arterial hypertension was defined as having blood pressure values ≥ 140 mmHg/90 mmHg measured at least twice and was assumed to be present in patients taking antihypertensive drugs. Diabetes mellitus was defined according to the 2019 clinical practice recommendations of the Expert

The diagnosis of PAD was classified in accordance with the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guidelines.Stroke was defined as a neurological deficit after 24 hours, as evaluated by a neurologist or internist,

All patients with stenosis > 55 % in one or more vascular districts and moderate-to-severe cardiovascular risk profile underwent CCTA to identify atherosclerotic coronary disease. Cardiovascular risk profile was calculated based on the ESC Guidelines risk score carts (very high risk: > 10%; high risk: 5%–10%; moderate risk: 1%–5%; low risk: ≤ 1%) on the basis of the presence of documented CVD, diabetes mellitus and chronic kidney disease (CKD). (17)

The present study was conducted in collaboration with the Unit of Radiology at Deba General Hospital, Tabook KSA. After being provided with information about the purpose of the study, the US Examinations were carotid duplex ultrasound machine, with a 3.5–7.5-MHz linear and convex transducer (SIEMENS, GE). included longitudinal and transverse examinations of the carotid arteries, abdominal aorta and the femoral-popliteal arteries. Both diameter reductions were measured and calculated at the site of maximal stenosis. All measurements were made on frozen, enlarged images (2×) at the end of a heart cycle (end diastole). UVE were performed by two cardiologists who specialised in vascular ultrasonography.

Atherosclerotic plaque was defined as focal echogenic structures encroaching into the vessel lumen, where the carotid intima media thickness (C-IMT) was greater than 1.2 mm C-IMT is the distance between the intima and the media tunica of the vessel examined. The high reproducibility of the examination, low invasiveness and its close correlation in predicting adverse cardiac events make C-IMT an effective and reproducible marker of atherosclerosis. These cut-offs were chosen, as they had been used in previous randomised clinical trials.

After UVE, demographic and lifestyle characteristics, medical history, data from physical examination and laboratory examinations were collected. Laboratory data was measured at the Analysis Laboratory at Deba General Hospital, Tabook KSA. All investigators and laboratory personnel were blinded to the patient's atherosclerotic disease.

Table I: Clinical and laboratory variables of patients

Variable	Characteristic
Age	Demographic and lifestyle
	Gender
	Height
	Weight
	Cigarette-smoking
Hypertension	Medical history
	Diabetes mellitus
	Family history of atherosclerosis
	Dyslipidaemia
	Prior acute myocardial infarction
	Angina pectoris
	Peripheral arterial disease
	Prior cerebral accident
	Current medications
Blood pressure	Physical examination
	Body mass index
Total cholesterol	Laboratory data
	High-density lipoprotein cholesterol
	Low-density lipoprotein cholesterol
	Triglycerides
	High-sensitivity C-reactive protein
	Fibrinogen
	Uric acid

Published literature shows that the amount of calcium present in the coronary arteries is related to the degree of CAD and the consequent risk of developing adverse coronary events It is widely known that coronary

calcifications share the same risk factors for atherosclerosis, and that changes in lifestyle and the introduction of lipid-lowering drugs may reduce their levels.

Going forward from this premise, Agatston assessed the amount of calcium in the coronary arteries using CCTA. In the past few years, this noninvasive measurement has been confirmed as a promising technique for identifying clinical and subclinical coronary stenoses. In particular, the risk of developing cardiovascular events has been shown to increase significantly when the score of Agatston exceeds a value of 400.

In our study, in accordance with standardised protocols, CACS was performed prior to coronary angiography. In fact, calcified atherosclerotic plaques can be displayed on CCTA even without the use of endovenous contrast agents. Investigators blinded to patient characteristics were to conduct offline analysis using automated computerised software programmes that employed the Agatston scoring method, with a threshold of 130 HU. (25) The calcium score percentile based on age and gender was calculated using CACS distributions from the Multi-Ethnic Study of Atherosclerosis. (26) This was performed using a web-based calculator (http://www.mesa-nhlbi.org/Calcium/input.aspx). For patients < 45 years old, '45 years' was used for the calculation of the calcium score percentile.

CCTA was conducted during contrast enhancement using prespecified protocols, as recommended by the scanner's manufacturers, during a single breath hold with prospective electrocardiographic gating, as appropriate. (27) According to standardised protocols, CCTA is performed during inspiratory apnoea and an elevated heart rate can limit the spatial resolution of its image. (24) For this reason, for all patients evaluated using CCTA, examination was done with heart rate in the range of 60–65 beats per minute. All CCTA examinations were assessed by two observers with extensive training in cardiac imaging. The examiners – radiologists and cardiologists, in particular – were blinded to the patient's characteristics.

The presence of two specialists for the execution and reporting of examination enabled, on the one hand, integration of medical knowledge and, on the other, greater emphasis on scientific interest vis-à-vis CCTA. Angiograms were reported using the 15-segment model. (28)

We defined significant stenosis due to CAD as stenosis > 70% in one or more major epicardial vessels or stenosis > 50% in the left main stem. Luminal cross-sectional area stenoses were classified as normal (< 10%), haemodynamically insignificant (10%–49%), intermediate (50%–70%), significant (≥ 70%), or total or subtotal occlusion (100%). Study participants were grouped into three atherosclerotic categories on the basis of the affected territories: carotid; aortic; and femoral.

The statistical significance of differences was examined using analysis of variance for continuous variables and the chi-square test for categorical variables. Associations between demographic variables, lifestyle, medical history and laboratory characteristics, and the three atherosclerotic categories were examined using logistic regression models. A p-value < 0.05 was considered to be statistically significant. Data was analysed using SPSS version 10.0 for Windows (SPSS Inc, Chicago, IL, USA).

3. Results

The mean or percentage values for the various demographic variables and established CVD risk factors are summarised by category of PVA in Table II. Among 515 patients enrolled in this study, 372 patients had atherosclerotic plaque while 143 patients only had increased C-IMT (C-IMT < 1.2 mm). As indicated earlier, only patients with ultrasonographic evidence of stenosis over 50% were subjected to further evaluations (e.g. CACS and CCTA) and therefore the 143 patients with C-IMT < 1.2 mm were excluded from subsequent imaging examinations.

Table 2: Demographic characteristics and cardiovascular risk factors of patients with polyvascular disease (n = 372).

Variable					%		
Single vessel disease)			Double vessel disease)			Triple vessel disease	
Carotid	Aortic	Femoral	Carotid aortic	Carotid femoral		Aortic femoral	Carotid aortic femoral
Demographic (no.)	95.0 (%)	30.0 (%)	50.0 (%)	45.0 (%)	40.0 (%)	20.0 (%)	70.0 (%)
Age (yr)*	60.6 ± 10	61. ± 11	60 ± 13	60 ± 12	61 ± 12	60 ± 11	6 ± 10

	Carotid	Aortic	Femoral	Carotid aortic	Carotid femoral	Aortic femoral	Carotid aortic femoral
Demographic (no.)	95.0 (%)	30.0 (%)	50.0 (%)	45.0 (%)	40.0 (%)	20.0 (%)	70.0 (%)
Age (yr)*	60.6 ± 10	61. ± 11	60 ± 13	60 ± 12	61 ± 12	60 ± 11	6 ± 10
Men/women†	5	6	4	7/6	5/9	6/7	8/5
Body mass index (kg/m2)*	26.0 ± 3.2	28.0 ± 2.1	28.6 ± 2.1	28.6 ± 2.1	26.0 ± 3.2	28.0 ± 2.1	28.6 ± 2.1
Smoking	21.0	25.0	24.0	34.0	41.0	32.0	53.0
Medical history							
Hypertension	8.0	6.0	5.0	7.0	8.0	12.0	15.0
Diabetes mellitus	15.0	10.0	11.0	28.0	24.0	29.0	44.0

Angina or myocardial infarction	2.0	1.0	1.0	2.0	1.0	1.0	2.0
Hyperlipidaemia	1.0	1.0	1.0	2.0	2.0	2.0	4.0
Family history							
Atherosclerosis	3.0	1.0	3.0	2.0	1.0	2.0	4.0
Stroke	1.0	1.0	1.0	1.0	1.0	1.0	3.0
Chronic kidney disease	0.0	0.0	0.0	1.0	0.0	1.0	1.0

Data presented as mean ± standard deviation. †Data presented as no.

The uses of drugs for the treatment of several cardiovascular risk factors were comparable among various patient groups. The patients enrolled were homogeneous for the presence of risk factors and extent of medical treatment.

Among 16 patients with atherosclerotic plaque, 15 had single vessel disease (or, atherosclerotic plaque localised only in the carotid, aortic or femoral district) and 10 patients had double vessel disease or triple vessel disease, along with ultrasonographic stenosis > 50%, and underwent CCTA. The coronary stenosis categories in this subset of patients were normal, haemodynamically insignificant (non-obstructive) lesions, intermediate stenosis, significant lesions 26.6%) and total artery occlusion 3.7%). Based on the coronary vessels involved, patients had single coronary disease, 41.0%; involving the left coronary artery, right coronary artery and proximal circumflex artery), double coronary disease, 42.0% and triple coronary disease 17.0%.

The odds ratios and 95% confidence intervals for having PVA (Table III) for selected risk factors, including inflammatory markers and plasma lipid levels, indicate the extent of polyvascular disease in the study population. CACS was significantly higher among patients with double vessel disease ($p < 0.01$) and triple vessel disease ($p < 0.001$) when compared to those with single vessel disease.

4. Discussion

Atherosclerosis is the leading cause of morbidity and mortality worldwide, and is expected to be the primary cause of death until the year 2020 despite ongoing efforts to extend primary and secondary prevention for high-risk individuals. (Atherothrombotic diseases are currently referred to as polyvascular disease

The increased awareness of the spread of atherosclerosis-related diseases has improved the development of techniques that enable early diagnosis and appropriate cardiovascular risk stratification. The study of atherosclerotic plaques can be performed using invasive methods, such as intravascular ultrasonography and optical coherence tomography, as well as noninvasive methods, such as ultrasonography, magnetic resonance imaging and CCTA. Based on the assumption that atherosclerosis is a polyvascular pathology by definition, the use of all these methods allowed, over the years, correlation of the presence of atherosclerotic lesions in different parts of the body and the identification of effective subclinical markers.

Our study, which was part of this line of research, confirms the role of CCTA in providing high-resolution images of the coronary anatomy. (32) The results of our study were along expected lines, as we found that a high prevalence of CAD was detected by CCTA in patients with PVA involving two or three districts with coronary stenosis over 50% and high/very high cardiovascular risk scores. This data emphasises the diagnostic accuracy of the technique, confirming, on the one hand, the high sensitivity of CCTA in highlighting CAD and, on the other, the correlation between the two noninvasive approaches of ultrasonography and CCTA.

Our result is in perfect agreement with the published literature. In fact, a study conducted by Cohen et al (33) compared the presence of carotid disease, evaluated using ultrasonography, and the presence of CAD, evaluated using CCTA. It showed that carotid plaque in conjunction with C-IMT correlates closely with the severity of coronary calcifications identified using CCTA.

We also demonstrated a good correlation between CACS and PVA. CACS correlates significantly with the degree of disease and the number of vessels involved, and was associated with extension and severity of CAD. Therefore, our study also emphasised the high positive predictive value of PVA, evaluated by ultrasonography, for predicting the presence of coronary atherosclerosis. Indeed, higher values of CACS were demonstrated in patients with double vessel disease and triple vessel disease in our study.

Our study confirmed the important role of CACS, when evaluated using CCTA, as an indicator that determines the risk of cardiac events. This result is in perfect agreement with data in the literature, which demonstrate that the absence of coronary calcification is related to a better prognosis and lower risk of developing coronary events. This parameter is easy to perform, inexpensive and easily reproducible. (34)

Indeed, CACS received a recommendation of IIa by ACCF/AHA for risk stratification in asymptomatic individuals in the intermediate risk class (Framingham risk score 10%–20%). (35) In patients at low or high cardiovascular risk, evaluation of CACS is not required.

However, CACS is a parameter that continues to have many uncertainties associated with it. First, a high value of CACS is not closely related to equally significant coronary stenosis. Second, the absence of a high value of CACS does not completely rule out the possibility of CAD, and, conversely, CACS cannot comment for those plaques that are non-calcified or partially calcified. (36)

In fact, for this reason, a major limitation regarding the diagnostic accuracy of CCTA is precisely coronary calcifications. The presence of calcium in the coronary arteries (in particular, CACS ≥ 400 or CACS ≥ 600) significantly reduces the specificity of the CCTA. (36) On the basis of this affirmation and the results obtained from our study, in which patients with double vessel disease and triple vessel disease obtained a higher CACS, we confirmed that CCTA had a negative predictive value, as widely described in the scientific literature. (37) It has been widely demonstrated that the sensitivity of CCTA in identifying severe stenosis is very high; on the contrary, the specificity tends to be lower due to the tendency of CCTA to overestimate stenosis, especially in calcified plaques. (24) CCTA, in fact, is indicated for patients with low-to-intermediate risk of CAD because a negative result could exclude, with significant probability, the presence of CAD. Equally, in patients at high risk for CAD, CCTA is unnecessary not only because it cannot add any information to the high pretest probability of CAD but also as it may require a subsequent coronary angiography, which is still considered to be the gold standard for the identification of coronary stenosis.

However, in recent years, renewed interest into the development of new technologies has expanded the clinical application of CCTA. The combined use of CCTA as an imaging technique and as fractional flow reserve (FFR) provides more information in patients with intermediate stenosis. (38) The FFR is defined as the ratio between maximal flow in stenotic vessel and maximal flow threshold in the normal vessel. A value of FFR < 0.8 is considered suggestive for ischaemia (39). For this reason, patients with intermediate coronary stenosis and FFR < 0.8 can benefit from revascularisation; conversely, the presence of FFR > 0.8 allows the adoption of conservative medical therapy.

Noninvasive imaging methods have been used to evaluate early signs of atherosclerosis. However, brightness-mode ultrasonography and cardiac magnetic resonance imaging do not enable complete evaluation of the coronary arteries. (40,41) Conventional coronary angiography and myocardial perfusion imaging imperfectly depict atherosclerosis, whether in its earlier stages or when the disease is mature but has not yet compromised luminal integrity by means of positive remodelling.
Our study confirms the important role of plasma lipid profiles and inflammatory markers in the pathogenesis of the atherosclerotic process, with a significantly higher serum concentration of total cholesterol, LDL-C, triglycerides and uric acid being seen among patients with PVA. For this reason, the administration of lipid-lowering therapy would reduce the progression of carotid atherosclerotic plaque. These findings suggest that the first and earliest manifestation of the atherosclerotic process characterised by plaque depends partly on the presence of an abnormal plasma lipid profile, with high concentrations of LDL-C and triglycerides. The plasma lipids pattern of patients with PVA was associated with an abnormal lipid profile that had significantly higher concentrations of LDL-C and triglycerides. We also identified a strong positive association between values of the inflammatory markers tested in our study and PVA, a finding that is in agreement with other studies in the literature. (42) A progressive increase was particularly found to be related to the interested districts of atherosclerotic plaque. This increase was independent of variables, such as age, body mass index and plasma lipid levels, on logistic regression analyses. This strong positive relationship may represent an important indicator of the oxidative stress and proinflammatory milieu involved in the atherosclerotic process.

Similar to earlier studies, we confirmed that arterial hypertension, diabetes mellitus, cigarette smoking, hyperlipidaemia, angina and myocardial infarction were the strongest and most significant risk factors for the development of PVA. Hypertension and diabetes mellitus have especially been shown to contribute to the remodelling of the arterial wall. These results were in accord with the findings of a community-based study in Taiwan that involved 3,602 participants, which demonstrated that hypertension was a major determinant of carotid atherosclerosis, particularly among patients aged over 35 years.

In summary, our study confirmed the known risk factors of PVA, such as hypertension, diabetes mellitus, cigarette-smoking, a positive family history of atherosclerosis or stroke, and elevated inflammatory markers (e.g. uric acid, hs-CRP and fibrinogen), which may represent a risk factor profile of individuals at the highest risk of developing CAD, when evaluated using CCTA. However, also noteworthy was the negative predictive value of CCTA for excluding the presence of coronary stenosis or ischaemia. (39) These findings suggest that the use of CCTA maybe erroneous and off-label for asymptomatic patients with PVA. Notwithstanding such reservations, in view of the spread of CVD and the importance of early detection to undertake targeted therapy, the clinical application of CCTA among patients with PVA is likely to rise. Further trials are warranted to extend the use of CCTA to other subsets of patients at risk of CAD.

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