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ORIGINAL ARTICLE

Aortic stiffness improves the prediction of both diagnosis and severity of coronary artery disease

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Elective coronography has low diagnostic yield for obstructive coronary artery disease (CAD). We aim to determine whether non-invasive aortic stiffness assessment improves diagnostic accuracy of CAD screening by reducing the number of false-positive results from the cardiac stress test. A cross-sectional study was conducted from January 2013 to September 2014 in our medical center. Electrocardiogram (ECG) stress test coupled with nuclear imaging was performed in 367 consecutive patients routinely followed for myocardial ischemia screening. Aortic pulse wave velocity (PWV) was assessed by applanation tonometry in the overall population. Forty-two patients underwent elective coronography because of ischemia. Theoretical PWV was calculated according to age, blood pressure and gender. The results were expressed as an index ((measured PWV–theoretical PWV)/theoretical PWV) for each patient. Ten patients presented with obstructive CAD, 16 patients had non-obstructive CAD and 16 patients had normal coronary angiography. PWV index and severity of CAD were positively correlated ($P=0.001$). All patients with obstructive CAD had a positive PWV index. When considering the PWV index retrospectively, the false positive results of cardiac stress test were significantly reduced ($P<0.001$). Twenty-three procedures may have been avoided in the present study cohort. The salient finding of this study was that in patients with known or suspected CAD, routinely followed aortic PWV index may be considered clinically useful for reducing the rate of unnecessary invasive angiographies. The clinical relevance of this individualized decision approach should be confirmed in a large-scale study. Prospective studies have the potential to evaluate the PWV index as a marker of CAD.
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Keywords: aortic stiffness; atherosclerosis; coronary artery disease screening

INTRODUCTION

Although the survival rate of patients with coronary heart disease has been steadily improving,[1] ischemic heart disease remains a worldwide public health problem.[2] Symptomatic coronary artery disease (CAD) and silent myocardial ischemia are both predictive of the risk of myocardial infarction and sudden death and therefore represent a crucial target of cardiovascular (CV) screening.[3,4] Invasive coronary angiography is considered justified when clinical evaluation associated with non-invasive cardiac testing suggests a high risk of obstructive coronary lesions. However, only slightly more than one third of patients without known CAD who underwent elective cardiac catheterization had obstructive coronary artery lesions.[5] Better strategies for CAD screening are required to reduce the unnecessary angiography rate and improve patient care.

Because of local availability and expertize, myocardial perfusion scintigraphy by single-photon emission computed tomography (SPECT) coupled with electrocardiogram (ECG) stress test was used in this study as a screening test for the assessment of inducible myocardial ischemia in at-risk patients. A large body of evidence supports the prognostic value of stress functional imaging with SPECT[6] for future cardiac events. However, positive and negative predictive values for obstructive CAD are considered to be 53 and 83%, respectively.[7] False positive results of a cardiac stress test may result in patient exposure to unnecessary risk during invasive angiography, whereas inconclusive or false negative results may lead to an underestimation of CAD and subsequent maladaptive medical management. In particular, significant multivessel CAD may lead to uniform tracer uptake due to "balanced" ischemia.[8]

Because of the variability in symptoms, clinical characteristics among patients and results obtained from non-invasive cardiac tests with substantial imperfections, there is often no single correct diagnosis approach to any given patient. Anatomical testing with the use of coronary computed tomographic angiography (CTA) has the potential to reduce unnecessary invasive procedures as recently highlighted in a large cohort of patients with suspected CAD. However, over a median follow-up period of 2 years, the authors concluded that a strategy of initial anatomical testing did not improve clinical outcomes compared with functional testing.[9] A non-invasive

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complementary measure of subclinical arterial disease may improve the diagnostic accuracy of cardiac stress test and subsequent patient management in at-risk populations. In particular, aortic stiffness is increasingly considered a functional and structural marker of cumulative exposure to all CV risk factors and a surrogate CV end point.[10–12] Carotid-femoral pulse wave velocity (PWV) is considered the gold standard for direct, non-invasive assessment of aortic stiffness and has independent predictive value for primary coronary events.[11,12] Previously, in a population of patients with advanced chronic kidney disease, aortic PWV was correlated with the extent and severity of coronary atherosclerosis.[13] We aimed to explore relationships between aortic stiffness and CAD in a cohort of patients without end-stage-renal disease routinely followed for CV screening.

Since age, gender and blood pressure (BP) are strong determinants of both aortic stiffness[14] and CAD,[3] a PWV index was calculated to determine the individual relevance of aortic stiffness assessment for CAD screening. This index was calculated as ((measured PWV–theoretical PWV)/theoretical PWV)[15] to identify those patients with increased aortic stiffness independent of age, mean BP and gender. The purpose of the present cross-sectional study was: to assess retrospectively the diagnostic accuracy of the ECG stress test coupled with myocardial functional imaging by SPECT (called the cardiac stress test) in patients with known or suspected CAD who underwent elective coronary angiography in our medical unit; to assess the correlation between aortic PWV index and the severity of CAD reported by coronary angiography; to determine whether aortic PWV index improves the diagnostic accuracy of non-invasive cardiac stress test by reducing the number of false-positive results.

METHODS

Overall population cohort

From January 2013 to September 2014, 399 consecutive patients, men and women, with or without previously identified CV events were eligible in this cross-sectional study during their routine follow-up at the Paris Hôtel-Dieu University Hospital. All patients were recruited after a visit in the Diagnosis and Therapeutics Center at Hôtel-Dieu University Hospital. The majority of patients had routine CV follow-up in our medical center, and the others were referred by their general practitioner for a CV check-up. Each patient provided informed consent for additional non-invasive hemodynamic measurements and data collection at the day hospital for CV screening. Exclusion criteria were age under 18 years, atrial fibrillation and medical conditions that contraindicated an exercise stress test.[16] Thirty-two patients were excluded due to missing PWV data (aortic PWV measurement has not been performed successfully because of frequent extrasystoles or poor quality waveforms). The overall population cohort was therefore composed of 366 patients. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The study was registered in the French National Agency for Medicines and Health Products Safety (No. 2013-A00227-38) and was approved by the locally appointed ethics committee.

Study cohort

From the overall population cohort, 42 patients underwent elective coronary angiography. A multidisciplinary decision for coronary angiography was proposed for each of the 42 patients according to the probability of CAD based on age, gender, symptoms and the results of cardiac testing.[17] Patients with a history of myocardial infarction or percutaneous coronary intervention were not excluded because the cardiac stress test was part of their routine follow-up as a guiding decision for a new, invasive coronary angiography. No patient had a history of surgical coronary revascularization. Three of the 42 patients included in the study cohort underwent CTA instead of invasive coronary angiography because of the relatively low likelihood of CAD associated with an inconclusive cardiac stress test. This multidisciplinary decision was based on the main clinical advantage of CTA related to its high negative predictive value, allowing the exclusion of obstructive coronary lesion.[18]

Clinical and hemodynamic parameters

Information compiled from the questionnaire filled out at inclusion in the day hospital for CV screening included gender, age, body mass index (BMI, weight in kilograms divided by the square of the height in meters), family history of premature CV events, personal history of dyslipidemia, hypertension, diabetes, smoking habits, medications and previous diseases. Hypertensive patients were all receiving antihypertensive drug treatment. Dyslipidemia was defined as a total/HDL cholesterol ratio >5 or the presence of a hypocholesterolemic drug. Previous CAD was defined as past medical history of documented myocardial infarction, coronary revascularization or epicardial CAD diagnosed during coronary angiography for patients with symptoms or typical electrocardiographic modifications. Previous cerebrovascular disease and peripheral arterial disease were defined as scan imaging-documented stroke for cerebrovascular disease, ankle-brachial pressure index value <0.90, and imaging-documented atherosclerotic vascular disease, including asymptomatic severe carotid artery stenosis, peripheral vascular disease and abdominal aortic aneurysm or arterial revascularization.

Laboratory parameters, including plasma glucose and glycated hemoglobin, cholesterol (total, low-density lipoprotein and high-density lipoprotein) and triglycerides, plasma creatinine and creatinine clearance rate were determined on the day of hemodynamic measurements.

Hemodynamic measurements were performed in the morning after an overnight fast in a supine position. Brachial systolic BP and diastolic BP were measured in both arms using an automatic BP monitor (OMRON 705 CP II IT) after 5 min of rest. Five measurements 2 min apart were averaged. Heart rate was recorded.

After BP determination, aortic PWV was performed non-invasively by applanation tonometry using an automatic device (SphygmoCor AtCor, Sydney, NSW, Australia) with simultaneous three-lead orthogonal ECG as previously described.[19] The reproducibility of these measurements, in our group and in others, has been previously published in detail.[20,21] Aortic PWV was calculated as the direct distance between carotid and femoral arteries divided by the time interval between the feet of the pressure waves at the recording sites. Pulse waveforms were obtained transcutaneously using applanation tonometry over the common carotid and femoral arteries. Direct distance was multiplied by a scaling factor of 0.8.[22]

A nomogram of aortic PWV was constructed, as previously described,[15] based on the overall population cohort of 367 patients, in order to determine theoretical aortic PWV values based on age, gender and mean BP. The equation derived was then applied to the subgroup of patients who underwent elective coronary angiography in order to obtain a theoretical aortic PWV value. The results were finally expressed as a PWV index defined as ((measured PWV–theoretical PWV)/theoretical PWV) adjusted on these three parameters for each of the 42 patients.

Coronary heart disease screening

The electrocardiogram stress test (during upright bicycle exercise) coupled with myocardial functional imaging by SPECT (cardiac stress test) was performed using a 1-day protocol for stress and rest studies.[16] Symptoms, 12-lead ECG, heart rate and BP were monitored continuously during the exercise test and for at least 5 min into the recovery phase.[23] A radiotracer injection (technetium 99 m labeled perfusion agent sestamibi) was performed intravenously at the peak of exercise. Electrocardiogram gating of the perfusion SPECT acquisition allowed quantitative assessment of the left ventricular function simultaneously with evaluation of left ventricular perfusion.[24] Perfusion abnormalities derived from the accepted 17-segment model for SPECT was used to evaluate the extent and severity of myocardial hypoperfusion and reversibility. Hybrid imaging modality with SPECT/computed tomography was used for attenuation correction.[25]

In patients who could not exercise adequately, a pharmacologic vasodilator stress test with dipyridamole was performed according to ASNC guidelines.[16] Discontinuation of antihypertensive medication with antianginal properties,

Table 1 Clinical, biological and hemodynamic parameters of the overall cohort ($N=367$)

	Patients who did not undergo coronography (N = 325)	*Patients who underwent coronography* (N = 42)	P-*value*
Gender/female (%)	141 (43)	7 (17)	**0.002**
Age (years)	61.7 ± 10.8	62.7 ± 10.3	0.55
Body mass index (kg m^{-2})	28.6 ± 4.8	27.7 ± 4.1	0.20
Smoking[a] (%)	135 (42)	25 (60)	**0.04**
Dyslipidemia[b] (%)	175 (54)	26 (62)	0.34
Hypertension (%)	244 (75)	30 (71)	0.75
Diabetes (%)	147 (45)	19 (45)	0.99
Coronary heart disease (%)[c]	43 (13)	12 (29)	**0.017**
Previous myocardial infarction (%)	17 (5)	5 (12)	0.17
Carotid plaque (%)	181 (56)	31 (76)	**0.03**
Left ventricular hypertrophy (%)	78 (24)	16 (39)	0.09
Previous stroke (%)	10 (3)	3 (7)	0.37
Peripheral arterial disease (%)	18 (6)	6 (14)	0.09
Glycated hemoglobin (%)	6.54 ± 1.46	6.57 ± 5.85	0.88
Creatinine clearance (ml mn^{-1})[d]	78 ± 21	83 ± 23	0.22
Heart rate (bpm)	71 ± 11	66 ± 10	< **0.001**
Betablocker treatment, *n* (%)	76 (23)	12 (29)	0.27
Brachial systolic BP (mmHg)	136 ± 15	135 ± 14	0.69
Brachial diastolic BP (mmHg)	79 ± 9	80 ± 11	0.54
Brachial PP (mmHg)	57 ± 13	55 ± 11	0.29
Mean arterial pressure (mmHg)	98 ± 10	98 ± 11	0.82
Aortic PWV (m s^{-1})	10.49 ± 2.50	10.72 ± 3.14	0.65
Aortic PWV index (%)	2.80 ± 19.63	3 ± 22.30	0.95

Abbreviations: BP, blood pressure; PP, pulse pressure; PWV, pulse wave velocity.
Continuous variables are presented as mean ± s.d.
Bold entries indicate a significant *P*-value.
[a]Past and current smokers.
[b]Patients receiving lipid lowering medication or classified as dyslipidemic.
[c]Coronary heart disease: previous documented myocardial infarction, coronary revascularization or epicardial coronary artery disease diagnosed during coronography for patients with symptoms or typical electrocardiographic modifications.
[d]Creatinine clearance estimated using MDRD formula. Aortic PWV index defined as the difference between observed and theoretical PWV divided by theoretical PWV for each subject.

such as b-blocker or calcium channel blocker, was left to the discretion of the referring physician. However, these medications were not discontinued in patients with known CAD.

Referring physicians reported stress test results as normal, equivocal/non-diagnostic or abnormal. A normal test was defined as a normal clinical and electrical stress test and uniform tracer uptake with normal regional wall motion. An abnormal ECG stress test was defined as clinically and/or electrically abnormal results. Abnormal myocardial perfusion SPECT was defined as inducible or fixed perfusion defects between the rest and stress images.

Obstructive coronary artery disease diagnosis

Elective invasive angiography was performed within 30 days of non-invasive cardiac testing. Results included location and degree of CAD as reported by the performing physicians. Consistent with prior studies,[5,26] CAD was defined by the degree of stenosis, which was classified as:

1. No apparent CAD: no stenosis >20%.
2. Non-obstructive CAD: ⩾1 stenosis ⩾20% but <70% (or <50% in the left main coronary artery).
3. Obstructive CAD: any stenosis ⩾70% or left main coronary artery stenosis ⩾50%.

Statistical analysis

Data were analyzed using R 3.1.3 software package. The characteristics of the study population were described as the means plus or minus standard deviation (± s.d.) for continuous variables. Categorical variables were described as numbers and proportions. Comparisons between groups were performed using non-parametric tests because of the skewed distribution of the variables. Alpha levels for significance were set at <5%. To determine theoretical PWV values, an equation for aortic PWV was constructed based on the overall population cohort ($N=367$). The factors included in the analysis were patient's age, mean BP and gender (male = 1 and female = 0). The following equation was subsequently applied to the patients who underwent coronary angiography in order to obtain a theoretical PWV value according to their age, BP and gender (gender was coded as 0 for women and 1 for men):

$$\text{Theoretical PWV} = -4.63 + 0.12 \times \text{age} + 0.07 \times \text{mean BP} - 0.01 \times \text{gender}.$$

A PWV index was calculated as ((measured PWV–theoretical PWV)/theoretical PWV). This index was considered to be abnormal when positive.

We analyzed screening performance on the cardiac stress test with and without PWV index by assessing positive predictive value for obstructive CAD screening among the 42 patients who underwent elective coronography. False-positive results on the cardiac stress test with and without PWV index were compared using McNemar's test.

RESULTS

Overall population cohort

In the overall population cohort, 317 patients presented with normal myocardial perfusion SPECT, and 50 patients presented with abnormal myocardial perfusion SPECT (with inducible or fixed perfusion defects between the rest and stress images). There was no correlation between PWV index and abnormal myocardial perfusion SPECT (Pearson's χ^2-test, $\chi^2=0.28$, P-value = 0.59). Clinical, biological and hemodynamic parameters of the overall population cohort are given in Table 1. Patients who underwent elective coronary angiography were more frequently men and past or current smokers compared to patients who did not undergo elective angiography. The patients more frequently had known CAD, carotid atherosclerosis and presented with lower heart rate. Age, peripheral hemodynamic measurements,

Table 2 Clinical, biological and hemodynamic parameters of the study cohort ($N=42$)

	Normal coronary angiography (N = *16)*	*Non-obstructive coronary lesions* (N = *16)*	*Obstructive coronary lesions* (N = *10)*	P-*value*
Gender/female (%)	6 (37.5)	0 (0)	1 (10)	0.99
Age (years)	61 ± 7	61 ± 14	68 ± 8	0.14
BMI (kg m^{-2})	28.6 ± 4.5	27.3 ± 4.1	27.0 ± 3.4	0.64
Smoking[a] (%)	9 (56)	8 (50)	8 (80)	0.16
Dyslipidemia[b] (%)	7 (54)	10 (63)	9 (90)	0.12
Hypertension (%)	8 (50)	12 (75)	10 (100)	**0.04**
Diabetes (%)	4 (25)	7 (44)	8 (80)	**0.03**
Coronary heart disease[c]	0 (0)	5 (31)	7 (70)	**0.002**
Previous MI	0 (0)	2 (13)	3 (30)	0.08
Carotid plaque (%)	11 (69)	11 (69)	9 (90)	0.53
LVH (%)	5 (31)	5 (31)	6 (60)	0.15
Previous stroke (%)	1 (6)	1 (6)	1 (10)	0.99
Peripheral arterial disease (%)	1 (6)	1 (6)	4 (40)	**0.02**
Glycated hemoglobin (%)	5.96 ± 0.85	6.87 ± 1.52	7.00 ± 1.29	**0.05**
Creatinine clearance (ml mn^{-1})[d]	81 ± 20	91 ± 22	68 ± 17	**0.014**
Heart rate (bpm)	66 ± 10	64 ± 9	69 ± 10	0.69
Betablocker treatment, *n* (%)	2 (13)	4 (25)	6 (60)	0.09
Brachial SBP (mmHg)	133 ± 12	134 ± 13	140 ± 19	0.75
Brachial DBP (mmHg)	80 ± 13	80 ± 10	78 ± 9	0.81
Brachial PP (mmHg)	53 ± 8	53 ± 9	62 ± 17	0.27
MAP (mmHg)	98 ± 12	98 ± 10	98 ± 10	0.99
Aortic PWV (m s^{-1})	9.09 ± 2.07	10.98 ± 3.40	12.94 ± 2.88	**0.003**
Aortic PWV index (%)	− 10.61 ± 19.69	7.44 ± 22.33	15.78 ± 15.87	**0.001**

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; MAP, mean arterial pressure; MI, myocardial infarction; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.
Continuous variables are presented as mean ± s.d.
Bold entries indicate a significant *P*-value.
[a]Past and current smokers.
[b]Patients receiving lipid lowering medication or classified as dyslipidemic.
[c]Coronary heart disease defined as previous documented myocardial infarction, coronary revascularization or epicardial coronary artery disease diagnosed during coronography for patients with symptoms or typical electrocardiographic modifications.
[d]Creatinine clearance estimated using MDRD formula. Aortic PWV index defined as the difference between observed and theoretical PWV divided by theoretical PWV for each subject.

aortic PWV and PWV index did not differ significantly between the two groups.

In the population of patients who did not undergo coronary angiography, PWV index (mean% ± s.d.) was not significantly higher in patients with known coronary heart disease than in those without (3.8 ± 23.4 and − 0.2 ± 18.5, respectively, $P=0.29$).

Study cohort

A minority of patients who underwent coronary angiography had obstructive CAD. Ten patients (24%) presented with obstructive CAD. Thirty-two patients (76%) presented with non-obstructive coronary artery lesions from which 16 patients (38% of the study cohort), including the three patients who underwent CTA, had normal coronary angiography.

The clinical, biological and hemodynamic parameters of the patients who underwent elective coronary angiography are given in Table 2. The presence of hypertension and diabetes was associated with the severity of coronary artery lesions. Previously, diagnosed CAD and peripheral arterial disease were more frequent in patients with obstructive coronary lesions. The estimated glomerular filtration rate (GFR) was negatively correlated with the severity of coronary artery lesions ($P=0.014$). Observed aortic PWV and PWV index were positively correlated with the severity of coronary artery lesions ($P=0.003$ and $P=0.001$, respectively) (Table 2 and Figure 1). Aortic PWV index was significantly increased in the 10 patients with obstructive CAD in comparison with the others ($P=0.004$). Aortic PWV index and GFR were not correlated ($P=0.24$). After adjusting for estimated GFR, aortic PWV index and presence of obstructive and non-obstructive coronary artery lesions remained significantly and positively correlated ($P=0.006$ and $P=0.011$, respectively).

Performance of screening test

The results of the ECG stress test coupled with myocardial functional imaging by SPECT were studied to retrospectively evaluate the diagnostic accuracy of the cardiac stress test for obstructive coronary lesions in the study cohort and the added value of aortic PWV index. Among the 42 patients who presented with an abnormal cardiac stress test and underwent elective coronography, 8 patients had an abnormal ECG stress test associated with abnormal myocardial perfusion SPECT and 34 patients presented with discordance between nuclear and clinical responses to stress.

Thirty-two patients presented with false positive results from cardiac stress test and thus underwent unnecessary coronography. The false-positive results on the cardiac stress test were evaluated when taking into account PWV index. The positive predictive value of the cardiac stress test with versus without PWV index was 53% (29–76%) versus 24% (12–39%), respectively. When considering the PWV index, false-positive results on the cardiac stress test were significantly reduced (McNemar test = 21, P-value <0.001) (Figure 2). The remaining false-positive results included nine patients with positive PWV index but without obstructive coronary artery lesions. All patients with obstructive CAD had a positive PWV index. Twenty-three procedures may have been avoided in the present study cohort. These results indicated that the aortic PWV index may be considered clinically relevant for reducing the rate of unnecessary angiographies.

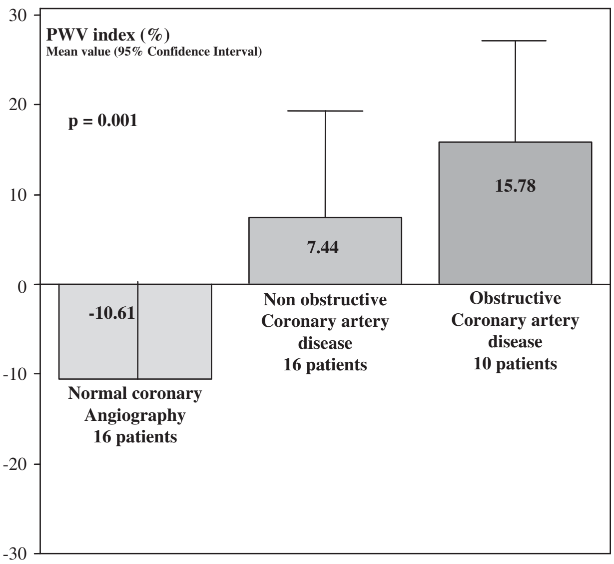

Figure 1 Aortic pulse wave velocity (PWV) index and severity of coronary artery disease.

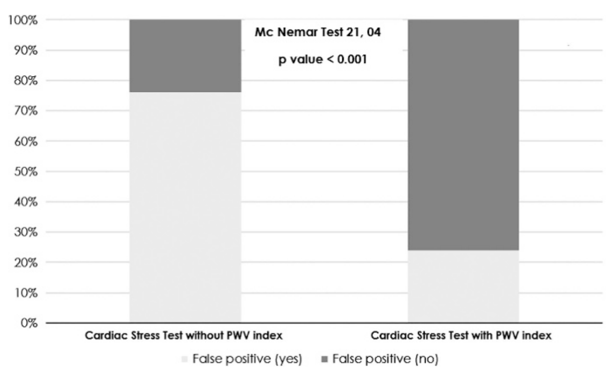

Figure 2 False positive results of the cardiac stress test with and without pulse wave velocity (PWV) index.

DISCUSSION

The salient finding of this study was that in patients with known or suspected CAD, routinely followed aortic PWV index may improve the diagnostic accuracy of non-invasive cardiac testing by reducing unnecessary invasive angiography rate without underestimating the presence of obstructive coronary artery lesions. Furthermore, the aortic PWV index was strongly correlated with the severity of CAD according to the degree of stenosis, independent of renal function. Thus, aortic stiffness may also be considered a marker of the presence of non-obstructive atherosclerotic coronary lesions, which represent a potential target for pharmaceutical interventions to prevent acute coronary syndrome.

Clinical relevance of aortic stiffness as a decision-making tool for the diagnostic use of coronary angiography

In our study cohort, a minority of patients who underwent coronary angiography (24%) had obstructive coronary lesions. No CAD was reported in 38% of the patients. These results are in line with previously published data highlighting the low diagnostic yield of elective coronary angiography.[5] Stress myocardial perfusion scintigraphy has emerged as one of the most commonly used functional imaging modalities for CAD screening.[27] The performance of SPECT in this study was comparable to that in others, and our results highlighted its imperfect level of accuracy in obstructive CAD screening.[7] Diagnostic application of SPECT is based on the ability to detect myocardial perfusion abnormality, which may be related to a hemodynamically significant and thus flow-limiting epicardial coronary stenosis. However, impaired myocardial perfusion during SPECT may also be related to microvascular dysfunction in patients with angiographically normal or minimally diseased coronary arteries.[28,29] In the present study cohort, 39% of patients presented with left ventricular hypertrophy, which may be associated with impairment of perfusion reserve independent of the presence of obstructive CAD.[30] Furthermore, our results highlighted the fact that clinicians are often confronted with marked discordance between nuclear and clinical responses to stress in patients with suspected CAD.

In the present study, the clinical relevance of aortic stiffness was studied as a potential non-invasive decision-making tool for further coronary angiography in patients with an abnormal cardiac stress test (abnormal stress test associated with abnormal myocardial perfusion SPECT or with discordant results between nuclear and clinical responses to stress). The aortic PWV index was significantly increased in patients with obstructive coronary lesions and was positively correlated with the severity of coronary artery stenosis. False-positive results on the cardiac stress test were significantly reduced when retrospectively considering the PWV index. The positive predictive value of the cardiac stress test with the PWV index was improved without underestimating the presence of obstructive CAD. In the present study, the PWV index may be considered clinically useful for reducing the rate of unnecessary angiographies (23 procedures may have been avoided in the study cohort).

Aortic stiffness is increasingly considered as a structural and functional marker of the integrated arterial damage caused by CV risk factors. This marker may also reflect individual susceptibility for both CV and cerebrovascular diseases, which cannot be captured on the basis of known traditional risk factors. In particular, arterial stiffness markers such as brachial-ankle PWV and cardio-ankle vascular index can be considered useful surrogate markers of cerebral small vessel disease and cerebral arteriosclerosis.[31] Carotid to femoral PWV, as a direct measure of aortic stiffness, is considered a marker of severity of CAD;[32] thus, the PWV index may be useful for CAD screening. Pathophysiological and observational evidence support the clinical relevance of aortic stiffness as a decision-making tool for the diagnostic use of coronary angiography. Aortic wall stiffening leads to increased PWV, which is considered the most important determinant of increased central systolic and pulse pressures in patients with preserved left ventricular ejection fraction.[33] Pathogenesis and progression of atherosclerotic damage appear to be driven by pressure pulsatility,[34] which is related to expression of adhesion molecules in the endothelium and lipid arterial wall infiltration. Observations from cross-sectional studies highlighted the correlation between central pulse pressure and presence and extent and severity of coronary artery plaque.[35–37]

Clinical implications and perspectives

Epidemiological and pathophysiological evidence support the relationship between aortic stiffness and the severity of coronary atherosclerosis. Large prospective data support the predictive value of aortic PWV for coronary events. In our study population, aortic stiffness assessment may have the potential to improve the diagnostic accuracy of the cardiac stress test. Increased PWV index may also be considered a marker of the presence of coronary atherosclerosis, either obstructive or non-obstructive. These considerations have potential clinical implications. First, to be clinically useful for CAD screening, non-invasive assessment of aortic stiffness must be relevant at the individual level. In the present study, theoretical PWV was defined on a population of patients routinely followed in our cardiovascular prevention unit. This population was representative of the cohort of patients who underwent coronary angiography. In each individual patient who underwent coronary angiography, the equation used to estimate theoretical PWV was based on patient's age, mean arterial pressure and gender, which are considered the most important determinants of aortic wall stiffening.[22] The calculation of a PWV index for each patient allows the estimation of the attributable part of aortic stiffness as a marker of CAD, adjusted on these three clinical parameters. Indeed, the relationship between an absolute value for PWV and the presence of CAD is particularly confounded by age and BP. This concept is also supported by previous findings. The cardio-ankle vascular index, a measure of arterial stiffness that can be calculated independent of BP during a single measurement, may represent a better surrogate marker of subclinical heart disease than an absolute PWV value.[38]

Second, except for acute coronary syndromes, it remains unclear if percutaneous angioplasty of severe coronary artery stenosis, in association with optimal medical therapy, improves outcomes in patients with stable CAD.[39] These results pointed to the concept of vulnerable plaque, which is considered a major precursor of acute coronary syndrome.[40,41] The severity of coronary stenosis evaluated during angiography appears inadequate to accurately predict the time or location of a future myocardial infarction.[42] Pending further methods to identify those coronary plaques that are on the evolution toward a vulnerable state for targeted therapeutic interventions, the pan arterial approach may serve as an aid to identify at-risk patients. The degree of pulsatile stress, which is closely related to aortic stiffness, appears to be associated with risk of plaque disruption.[43] Central pulsatility is considered the most powerful hemodynamic predictor of CV risk in coronary patients.[44] The aortic PWV index may therefore represent a candidate marker of arterial damage that may be indicative of the presence of vulnerable plaque prone to rupture.

Third, the clinical importance of non-obstructive CAD in primary prevention was recently highlighted in a large cohort of patients who underwent elective coronary angiography. Compared with patients with no apparent CAD, patients with non-obstructive lesions exhibited significantly greater 1-year risk of myocardial infarction and all-cause mortality.[45] In primary prevention, medical management of patients with non-obstructive coronary lesions should warrant further consideration. The presence of non-obstructive CAD in association with increased aortic stiffness may be indicative of a vulnerable population at risk for CV events.

Limitations

The present study has limitations common to cross-sectional designs, especially in establishing cause-effect relationships between aortic PWV index and severity of CAD or for considerations of coronary plaque vulnerability. The study cohort was representative of the patients followed-up in our medical unit. Most patients with obstructive coronary lesions more frequently had known CAD, which may explain the observed increased PWV values. However, in the population of patients without coronary angiography, PWV index was not significantly higher in patients with known stable coronary heart disease than in those without. We also observed that patients with obstructive coronary artery lesions presented with lower GFR. It has been previously indicated that the incidence and severity of CAD increase as GFR declines.[46] Furthermore, the degree of aortic stiffness is known to be negatively correlated with GFR in subjects with mild-to-moderate renal insufficiency.[47] In our study population, our results underscored that aortic PWV index and severity of CAD remained significantly correlated even after adjusting for GFR.

The definition of the patient population is critical for the evaluation of the clinical relevance of aortic PWV. In particular, carotid-femoral PWV assessment in patients with peripheral arterial disease has to be considered with caution in the presence of obstructive aorto-iliac disease.[48] In this study, the overall population cohort is not representative of a population hospitalized for peripheral arterial disease. Among the 24 patients with peripheral arterial disease, two patients had obstructive non-revascularized proximal and unilateral iliac disease. Femoral tonometry had been performed on the contralateral side, where the femoral pulse was palpated. Indeed, such occlusive lesions are expected to delay the pulse wave propagation and may result in a falsely low PWV.[48]

Calculation of an index is dependent on the theoretical PWV evaluation, which is expected to be different in another patient group. Estimation of theoretical PWV value has included a representative population of patients routinely followed for CAD screening in the present medical unit, which may strengthen the individual relevance of aortic stiffness assessment. The small number of patients who underwent elective coronary angiography may be the principal limitation in this study. However, our results underscored a significant reduction in false-positive results on a cardiac stress test when retrospectively considering the PWV index in the cohort of patients who underwent elective coronography. In an individualized decision approach, this index may thus have the potential to avoid unnecessary invasive procedures. These results provide insight regarding a new approach in invasive angiography decision-making and should be confirmed in a large-scale study.

Conclusions

The present results call for a large-scale study examining the relevance of the aortic PWV index in CAD screening in association with the currently recommended clinical practice. Pathophysiological and epidemiological evidence suggest that this marker of arterial damage may have the potential to improve patient care. This approach is expected to assist the physician in invasive angiography decisions in the CAD diagnostic pathway.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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