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Impact of aortic stiffness on myocardial ischaemia in non-obstructive coronary artery disease

Mai Tone Lønnebakken,[1,2] Ingeborg Eskerud,[1] Terje Hjalmar Larsen,[2,3] Helga Bergljot Midtbø,[2] Marina Victorovna Kokorina,[2] Eva Gerdts[1]

To cite: Lønnebakken MT, Eskerud I, Larsen TH, *et al*. Impact of aortic stiffness on myocardial ischaemia in non-obstructive coronary artery disease. *Open Heart* 2019;**6**:e000981. doi:10.1136/openhrt-2018-000981

The abstract has previously been presented in European Heart Journal 39(suppl_1) DOI: 10.1093/eurheartj/ehy563. P3652

Received 1 December 2018
Revised 3 April 2019
Accepted 14 April 2019

[1]Department of Clinical Science, University of Bergen, Bergen, Norway
[2]Department of Heart Disease, Haukeland University Hospital, Bergen, Norway
[3]Department of Biomedicine, University of Bergen, Bergen, Norway

Correspondence to
Dr Mai Tone Lønnebakken, Universitetet i Bergen Det medisinske fakultet, Bergen, Norway; mai.lonnebakken@k2.uib.no

ABSTRACT

Objective High aortic stiffness may reduce myocardial perfusion pressure and contribute to development of myocardial ischaemia. Whether high aortic stiffness is associated with myocardial ischaemia in patients with stable angina and non-obstructive coronary artery disease (CAD) is less explored.

Methods Aortic stiffness was assessed as carotid-femoral pulse wave velocity (PWV) by applanation tonometry in 125 patients (62±8 years, 58% women) with stable angina and non-obstructive CAD participating in the Myocardial Ischemia in Non-obstructive CAD project. PWV in the highest tertile (>8.7 m/s) was taken as higher aortic stiffness. Stress-induced myocardial ischaemia was detected as delayed myocardial contrast replenishment during stress echocardiography, and the number of left ventricular (LV) segments with delayed contrast replenishment as the extent of ischaemia.

Results Patients with higher aortic stiffness were older with higher LV mass index and lower prevalence of obesity (all p<0.05), while angina symptoms, sex, prevalence of hypertension, diabetes, smoking or LV ejection fraction did not differ between groups. Stress-induced myocardial ischaemia was more common (73% vs 42%, p=0.001) and the extent of ischaemia was larger (4±3 vs 2±3 LV segments, p=0.005) in patients with higher aortic stiffness. In multivariable logistic regression analysis, higher aortic stiffness was associated with stress-induced myocardial ischaemia independent of other known covariables (OR 4.74 (95% CI 1.51 to 14.93), p=0.008).

Conclusions In patients with stable angina and non-obstructive CAD, higher aortic stiffness was associated with stress-induced myocardial ischaemia. Consequently, assessment of aortic stiffness may add to the diagnostic evaluation in patients with non-obstructive CAD.

Trial registration number NCT01853527.

Key questions

What is already known about this subject?
Myocardial ischaemia in non-obstructive coronary artery disease (INOCA) have a multifactorial aetiology and is associated with an impaired prognosis.

What does this study add?
Higher aortic stiffness assessed by carotid-femoral pulse wave velocity is independently associated with INOCA.

How might this impact on clinical practice?
Assessment of aortic stiffness may add to the diagnostic evaluation of patients with stable angina and non-obstructive coronary arteries and may facilitate individualised treatment.

INTRODUCTION

Ischaemia in non-obstructive coronary artery disease (INOCA), characterised by myocardial ischaemia without flow-limiting stenosis by coronary angiography, is a common finding, particularly in women, and associated with an impaired prognosis.[1 2] The Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry reported a prevalence of non-obstructive coronary artery disease (CAD) of 30% and a twofold increase in 5-year cardiovascular morbidity and mortality.[3] A recent consensus document underlines the multifactorial aetiology and the lack of scientifically funded recommendations for management of INOCA.[4] Thus, better diagnostic algorithms and evidence-based risk assessment tools are needed for management of patients with INOCA.[5–7]

Aortic stiffness, assessed non-invasively as pulse wave velocity (PWV), is an established risk predictor in hypertension[8] and in an urban female population.[9] Increased aortic stiffness is also a predictor of presence, severity and prognosis of CAD in both general and high-risk populations.[10–14] Increased aortic stiffness is associated with increased systolic and reduced diastolic blood pressure (BP) in the aortic root due to earlier return of the reflectory pressure waves from the distal aorta.[15] This leads to increased left ventricular (LV) afterload and oxygen demand, reduced myocardial diastolic perfusion pressure and consequently myocardial ischaemia.[16 17] Thus, in a previous study of asymptomatic patients with diabetes, increased

aortic stiffness was associated with myocardial perfusion defects by single-photon emission computed tomography (SPECT) imaging.[18]

Whether increased aortic stiffness measured by PWV is associated with INOCA is less explored. Accordingly, we assessed the association between higher aortic stiffness and stress-induced myocardial ischaemia in patients with angina and non-obstructive CAD.

METHODS

Patient population

The current analysis was prospectively planned within the Myocardial Ischemia in Non-obstructive Coronary Artery Disease project, a cross-sectional observational study that included 132 patients with stable angina and non-obstructive CAD by coronary CT angiography. Inclusion criteria were stable angina for at least 6 months, presence of non-obstructive CAD by coronary CT angiography, age >30 years and presence of at least one cardiovascular risk factor. Exclusion criteria were significant coronary artery stenosis (lumen diameter reduction ≥50%) or normal coronary CT angiography, as well as clinically unstable angina, severe valve disease, mechanical valve prosthesis, arrhythmias, severe pulmonary disease or known allergies to ultrasound contrast. Carotid femoral PWV could not be measured in seven patients due to cardiac arrhythmias (atrial fibrillation or frequent premature extra beats), and these were excluded leaving 125 patients for the present analysis. Written informed consent was obtained from all study participants.

Cardiovascular risk factor assessment

All study participants reported cardiovascular risk factors, medical history and medication on a standardised questionnaire. Clinical examination and collection of fasting blood samples were performed in all. BP was measured three times in the sitting position following the European Society of Hypertension guidelines using a digital automatic sphygmomanometer Omron M4 (Omron Healthcare Co, Hoofddorp, the Netherlands), and the office BP was taken as the mean of the two last measurements.[8] Hypertension was defined as known hypertension, use of antihypertensive drugs or office systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg. Diabetes was defined as known diabetes or use of antidiabetic drugs. Hypercholesterolaemia was defined as total cholesterol >6.5 mmol/L or on statin treatment. Body mass index (BMI) was calculated as body weight in kilograms divided by height in metres squared. Obesity was defined as BMI ≥30 kg/m^2.

Carotid-femoral PWV

Carotid-femoral PWV was measured by applanation tonometry using the SphygmoCor device (AtCor, Medical, Sydney, West Ryde, Australia) by an experienced operator (MVK). Following current recommendations, pressure pulse waveforms from the right common carotid and femoral arteries were obtained transcutaneously, and the PWV was calculated as the transit time between the two arterial sites, determined in relation to the R-wave of the ECG and divided by the net distance between the two recording sites.[15] PWV in the highest population tertile (>8.7 m/s) was regarded as higher aortic stiffness.

Echocardiography

Conventional echocardiography was performed on a Philips ie33 (Philips Medical Systems) scanner following a standardised protocol. All echocardiograms were read offline on a workstation equipped with Image Arena software version 4.1 (TomTec Imaging Systems GmbH, Unterschleissheim, Germany) by the same experienced reader (MTL). Measurements were made according to the joint American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations.[19] LV mass was calculated by Devereux's equation and indexed for height in metres in the allometric power of 2.7. LV hypertrophy was defined by the prognostically validated cut-off values of LV mass index >46.7 g/m$^{2.7}$ in women and >49.2 g/m$^{2.7}$ in men.[20] Relative wall thickness was calculated as 2× posterior wall thickness/LV internal radius ratio. LV filling was assessed by the ratio between transmitral flow (E-wave) and mitral annular velocity (e′).

Myocardial contrast echocardiography was performed with real-time low-mechanical index imaging and destruction replenishment following current guidelines.[21 22] Ultrasound contrast agent (SonoVue, Bracco, Milan, Italy) was administered intravenously as 1 mL bolus followed by continuous infusion of 1 mL/hour using a rotating infusion pump (VueJet, Bracco, Milan, Italy). Myocardial perfusion was visually scored as normal or abnormal in the individual 17-segments of the LV using the apical 2-chamber, 3-chamber and 4-chamber views at rest and at peak dobutamine stress.[19] Stress-induced myocardial ischaemia was defined as presence of delayed contrast replenishment two heartbeats after flash at peak stress in any LV segment. The number of LV segments with delayed perfusion at peak stress was taken as a measure of the extent of myocardial ischaemia.

Coronary CT angiography

Prior to inclusion into the study, all patients had undergone coronary CT angiography by a 256-slice dual source CT scanner (Somatom Definition Flash, Siemens, Germany) with ECG triggered acquisition and intravenously iomeprol 400 mg I/mL contrast (Iomeron, Bracco, Milan, Italy). Coronary artery calcium score and degree of coronary artery stenosis were assessed by experienced readers following a modified 20-segment American Heart Association model.[23] High coronary artery calcium score was defined as a calcium score >100 Hounsfield units (HU). Non-obstructive CAD was defined as a lumen diameter reduction of 1%–49% in any coronary artery segment without any segments with ≥50% lumen diameter reduction and extent of non-obstructive CAD are expressed as the segment involvement score.[3]

Statistical analysis

Data management and analysis were performed using IBM SPSS Statistics V.24 (IBM Corporation, Armonk, New York, USA). Patients were grouped in tertiles of PWV, and the highest tertile (PWV >8.7 m/s) was regarded as high aortic stiffness. Patients with high aortic stiffness were compared with patients with normal aortic stiffness by unpaired Student's t-test and χ statistics as appropriate. Results are presented as mean±SD for continuous variables and percentages for categorical variables. The performance of PWV and calcium-score to detect stress-induced myocardial ischaemia is expressed and compared using receiver operating characteristics (ROC) curve and the area under the curve (AUC) with 95% CI. The association between higher aortic stiffness and stress-induced myocardial ischaemia was explored in univariable and multivariable logistic regression analysis, adjusting for known confounders and presented as OR with 95% CI. To further adjust for bias, propensity score matching for age, sex, systolic BP, hypertension, diabetes, smoking, hypercholesterolaemia, obesity, LV mass index, LV filling, calcium score and segment involvement score by coronary CT angiography was performed between cases with and without ischaemia. A two-tailed p value <0.05 was regarded as significant.

RESULTS

Patients' characteristics

Patients with high aortic stiffness were older and had higher BP, higher prevalence of hypercholesterolaemia and lower prevalence of obesity and familial premature CAD (all p<0.05), while there were no differences in sex, angina symptoms, prevalence of hypertension, diabetes, smoking or renal function (table 1). In patients with high aortic stiffness, a history of stroke and known peripheral artery disease was more common, and more patients used antiplatelet and statin treatment, while there were no differences in antihypertensive treatment between groups (table 1).

Table 1 Patients' characteristics

	Lower PWV	Higher PWV	P value
Age (years)	60±9	67±6	<0.001
Female sex (%)	63	49	0.127
BMI (kg/m^2)	28.0±4.9	27.1±3.8	0.268
Waist circumference (cm)	97±13	98±10	0.636
Obesity (%)	29	12	0.042
Chest pain (%)	79	71	0.335
Exertional dyspnoea (%)	63	68	0.568
Heart rate (BPM)	69±12	66±11	0.197
Systolic blood pressure (mm Hg)	130±14	143±18	<0.001
Diastolic blood pressure (mm Hg)	76±12	82±14	0.018
Hypertension (%)	70	83	0.118
Diabetes (%)	12	11	0.791
Hypercholesterolaemia (%)	41	61	0.031
Family history of premature CAD (%)	68	44	0.018
Current smoker (%)	18	11	0.587
Previous myocardial infarction (%)	1	3	0.559
Previous stroke (%)	1	11	0.017
Known peripheral artery disease (%)	3	14	0.016
Antiplatelet therapy (%)	37	65	0.006
Antihypertensive therapy (%)	53	64	0.267
Statins (%)	32	51	0.044
Serum-cholesterol (mmol/L)	5.1±1.3	4.8±1.1	0.225
Serum HDL (mmol/L)	1.5±0.5	1.5±0.4	0.751
Serum LDL (mmol/L)	3.3±1.2	3.1±1.0	0.354
Serum triglycerides (mmol/L)	1.52±1.06	1.41±0.79	0.525
Estimated GFR (mL/min/1.73 m^2)	87±15	84±12	0.380

BMI, body mass index;CAD, coronary artery disease;GFR, glomerular filtration rate;HDL, High Density Lipoprotein;LDL, Low Density Lipoprotein;PWV, pulse wave velocity.

Aortic stiffness and myocardial ischaemia

Stress-induced myocardial ischaemia was more prevalent, and the extent of ischaemia was larger among patients with high aortic stiffness, while there was no difference in coronary artery calcium score or segment involvement score by coronary CT angiography (table 2). LV mass index and LV filling was higher, but there were no significant difference in left atrial volume, LV ejection fraction, prevalence of hypertrophy and concentric LV geometry (table 2).

In univariable analysis, high aortic stiffness was associated with presence of stress-induced myocardial ischaemia (OR 3.82 (95% CI 1.69 to 8.62), p=0.001). In multivariable logistic regression analysis, higher aortic stiffness remained significantly associated with presence of stress-induced myocardial ischaemia independent of age, systolic BP, hypercholesterolaemia, obesity, LV mass index, LV filling, as well as calcium score and segment involvement score by coronary CT angiography (table 3). After adding propensity score matching between cases with and without myocardial ischaemia accounting for known covariables, aortic stiffness remained significantly associated with myocardial ischaemia, (OR 5.01, p=0.011).

In ROC curve analysis, PWV was a better predictor of stress-induced myocardial ischaemia (AUC 0.65 (95%

Table 2 Cardiovascular imaging characteristics

	Lower PWV	Higher PWV	P value
PWV (m/s)	7.4±0.9	10.9±2.4	
Coronary CT angiography			
Coronary artery calcium score (HU)	71±100	107±133	0.138
High calcium score (%)	22	36	0.104
Segment involvement score	2±1	3±1	0.297
Echocardiography			
Left atrium biplane volume (mL/m^2)	42±12	45±17	0.329
Intraventricular septum in diastole (cm)	1.1±0.2	1.2±0.2	0.013
LV end-diastolic dimension (cm)	4.5±0.5	4.5±0.6	0.994
LV end-systolic dimension (cm)	2.9±5.0	2.9±6.1	0.616
Posterior wall thickness in diastole (cm)	0.9±0.2	1.0±0.2	0.042
LV ejection fraction (%)	62±6	62±9	0.704
LV mass index (g/m$^{2.7}$)	38.5±8.2	42.5±10.8	0.042
Relative wall thickness	0.40±0.09	0.44±0.13	0.074
LV hypertrophy (%)	14	22	0.282
Concentric geometry (%)	29	42	0.149
Isovolumic relaxation time (ms)	79±18	84±15	0.104
LV filling	9.5±2.2	10.7±3.2	0.042
Myocardial contrast stress echocardiography			
Stress-induced myocardial ischaemia (%)	42	73	0.001
Number of LV segments with ischaemia	2±3	4±3	0.002

LV, left ventricular;PWV, pulse wave velocity.

CI 0.55 to 0.75), p=0.005) than coronary artery calcium score by coronary CT angiography (figure 1).

DISCUSSION

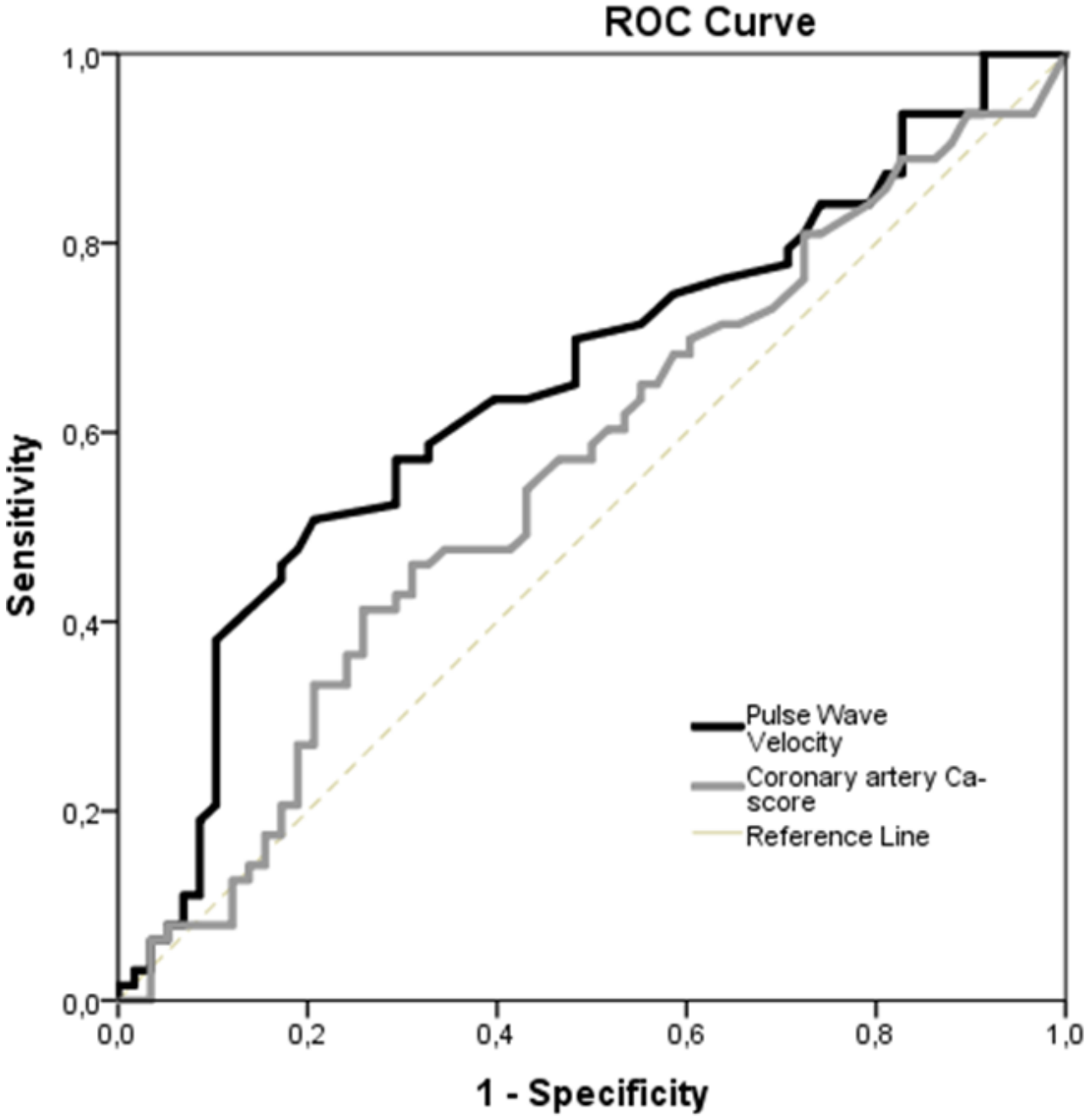
This study demonstrates for the first time the association of higher PWV with stress-induced myocardial ischaemia in patients with INOCA, suggesting that higher aortic stiffness may contribute to reduced myocardial perfusion during stress in such patients.

Aortic stiffness is an established risk predictor in hypertension[8] and associated with increased cardiovascular events and all-cause mortality rate in both hypertensive and general populations.[12 14] The prognostic value of aortic stiffness was also recently demonstrated in patients

Table 3 Covariables of higher aortic stiffness in patients with angina and non-obstructive CAD in multivariable logistic regression analysis

Variables	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Myocardial ischaemia	3.81	1.69 to 8.62	0.001	4.74	1.51 to 14.93	0.008
Age (years)	1.14	1.07 to 1.22	<0.001	1.12	1.04 to 1.22	0.005
Systolic BP (mm Hg)	1.05	1.03 to 1.08	<0.001	1.06	1.02 to 1.10	0.001
Hypercholesterolaemia	2.30	1.07 to 4.93	0.33	3.04	1.03 to 9.01	0.045
Obesity	2.88	1.01 to 8.22	0.048	1.58	0.41 to 6.22	0.508
LV mass index (g/m$^{2.7}$)	1.05	1.01 to 1.09	0.028	1.03	0.98 to 1.09	0.282
LV filling	1.19	1.02 to 1.38	0.024	1.00	0.81 to 1.24	0.981
Calcium score	1.00	0.99 to 1.01	0.110	1.00	0.99 to 1.01	0.903
Segment involvement score	1.15	0.88 to 1.49	0.307	1.18	0.79 to 1.78	0.420

BP, blood pressure;CAD, coronary artery disease; LV, left ventricle.



	AUC	95% CI	P-value
Pulse Wave Velocity (m/s)	0.65	0.55-0.75	0.005
Coronary artery Ca-score	0.56	0.45-0.66	0.276

Figure 1 ROC curve analysis for pulse wave velocity and coronary artery calcium score in assessment of myocardial ischaemia in patients with INOCA. Ca, calcium; INOCA, Ischaemia in non-obstructive coronary artery disease; ROC, receiver operating characteristics.

with ST-elevation myocardial infarction.[24] Experimental and clinical studies have suggested that aortic stiffening leads to reduced coronary flow and subendocardial ischaemia even in the absence of coronary artery stenosis.[25 26] The characteristic early return of the pulse wave reflections to the aortic root in aortic stiffness increases the systolic BP and the workload of the LV, thereby increasing the myocardial oxygen demand and lowering the ischaemic threshold in the myocardium.[15] In addition, the early pulse wave reflections in aortic stiffness reduces the diastolic perfusion pressure in the myocardium and causes a reduction in coronary artery flow. The duration of the diastole is also reduced due to the increased LV after load, further amplifying the reduction in myocardial blood flow.[15] Theoretically, these pathophysiological changes in combination with increased atheromatosis associated with aortic stiffness will contribute to development of myocardial ischaemia in patients with higher PWV, as demonstrated in the present study.

The Women's Ischemia Syndrome Evaluation study demonstrated that myocardial ischaemia may be present in non-obstructive CAD and that myocardial ischaemia in patients with non-obstructive CAD was associated with an impaired prognosis.[27 28] Recently, INOCA, the clinical syndrome of myocardial ischaemia in non-obstructive CAD, has been recognised as a diagnostic and therapeutic challenge.[1] In the present study, stress-induced myocardial ischaemia was identified in 52% of patients with symptomatic angina and non-obstructive CAD, pointing to the need for additional non-invasive cardiovascular imaging to identify patients with INOCA even in the presence of angina. Furthermore, our results add to current knowledge by demonstrating that higher PWV was closer associated with stress-induced myocardial ischaemia in non-obstructive CAD then calcium score and segment involvement score by coronary CT angiography. This suggest assessment of PWV may identify patients with symptomatic non-obstructive CAD with a high likelihood for stress-induced myocardial ischaemia.

Advances in anatomical and functional imaging may contribute to improvement in the diagnostic and prognostic evaluation in INOCA. Myocardial ischaemia in non-obstructive CAD has a multifactorial aetiology,[6] including microvascular and endothelial dysfunction. We have previously demonstrated the association between LV hypertrophy and myocardial ischaemia in hypertensive heart disease.[29] Of note, though both LV hypertrophy and aortic stiffness are regarded as hypertension-mediated target organ damage, high aortic stiffness was associated with stress-induced myocardial ischaemia independent of BP and LV mass index in the multivariable analysis. Interestingly, coronary artery calcium score was not associated with myocardial ischaemia in the present study, in line with previous studies demonstrating that non-calcified hypodense coronary artery plaques carries the highest cardiovascular risk.[30] In addition, as also demonstrated in our study, both PWV and prevalence of myocardial ischaemia increases with age. A previous study have established normal reference values for PWV in different age and BP categories based on a large European population.[31] However, among patients with angina and non-obstructive CAD, higher PWV was associated with myocardial ischaemia independent of age, and the association remained significant even after propensity score matching for major confounders including age.

In clinical practice, there is a lack of scientifically based recommendations for management of angina with non-obstructive CAD, including systematic assessment of stress-induced myocardial ischaemia. Considering the multifactorial aetiology of myocardial ischaemia in such patients, the need for an accurate diagnosis and individualised treatment is emphasised by the impact of myocardial ischaemia on quality of life and prognosis.[4 5]

Study limitations

This is a small study including 125 patients increasing the risk of type 2 statistical errors. Since this is a cross-sectional study, no causal mechanisms can be identified. Furthermore, the study included only patients with cardiovascular risk factors clinically referred for coronary CT angiography, introducing a possible selection bias. The results should therefore be generalised to less selective populations with caution. However, our study adds to current knowledge by demonstrating that higher PWV is associated with an increased risk for presence of INOCA, underlining the need for larger follow-up studies to further evaluate the role in diagnosis and risk stratification of aortic stiffness assessment by PWV in patients with angina and non-obstructive CAD.

CONCLUSION

In patients with stable angina and non-obstructive CAD by coronary CT angiography, higher aortic stiffness was associated with stress-induced myocardial ischaemia. This suggests that assessment of aortic stiffness may add to the diagnostic evaluation in patients with non-obstructive CAD. However, further research is needed to evaluate if assessment of aortic stiffness can become a diagnostic and risk stratification tool in non-obstructive CAD.

Acknowledgements We would like to thank Liv Himle (RN), Britt Gjellefall (RN), Liqun Zhang (staff engineer) and Synnøve Ygre Hauge (RN) for technical assistance with data collection, registration and participant management.

Contributors MTL has contributed to study design, acquisition, analysis and interpretation of data, drafting the article and final approval of the article. IE, THL, MVK and HBM have contributed to the acquisition of data, revising the article for important intellectual content and final approval of the article. EG have contributed to study design, supervision, revising the article for important intellectual content and final approval of the article. All authors are accountable for all aspects of the work and take responsibility for the accuracy and integrity of the work.

Funding Financial support was obtained from the MedViz Consortium, a collaboration between the University of Bergen, Haukeland University Hospital and Christian Michelsen Research, all Bergen, Norway and the Western Norwegian Regional Health Authorities. None of the sponsors had any involvement in study design, data collection, analysis or interpretation of data, writing of the report or in the decision to submit the paper for publication.

Disclosure The authors report no conflict of interest.

Competing interests None declared.

Patient consent for publication Not Required

Ethics approval The Myocardial Ischemia in Non-obstructive CAD study was approved by the regional ethics committee for medical research and conducted according to the Helsinki declaration.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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