Association of echocardiographic measures of left ventricular diastolic dysfunction and hypertrophy with presence of coronary microvascular dysfunction

Iryna Dykun [1],*, Luisa Kärner [1], Ihab Mahmoud [1], Stefanie Hendricks [1], Matthias Totzeck [1], Fadi Al-Rashid [1], Tienush Rassaf [1], Amir A. Mahabadi [1]

The Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center, University of Duisburg-Essen, Essen, Germany

A R T I C L E   I N F O

A B S T R A C T

Background: Coronary microvascular dysfunction (CMD) is a common disorder, leading to symptoms similar to obstructive coronary artery disease. We aimed to determine whether measures of left ventricular (LV) diastolic function and hypertrophy may predict presence of CMD.
Methods: We retrospectively included patients undergoing diagnostic coronary angiography and transthoracic echocardiography, excluding patients with obstructive coronary artery disease, previous revascularization therapy, moderate or severe mitral valve disease, or atrial fibrillation. The following markers of LV diastolic function and hypertrophy were assessed: E- and A-wave velocity, E-wave deceleration time, E/A- and E/E′-ratio, left atrial area, left LV mass index, LV ejection time (LVET) and mitral valve closure to opening time. Logistic regression analysis was used to determine the association of echocardiographic parameters with presence of CMD.
Results: From 378 patients (mean age ± SD 59.7 ± 13.6 years, 45.6% male) included, the majority had CMD (n = 293, 77.5%). Patients with CMD were older (60.5 ± 13.4 years vs. 56.9 ± 14.3 years, p = 0.03), were less frequent male (42.3% vs. 57.0%, p = 0.02), and had higher systolic blood pressure (137.9 ± 25.7 mmHg vs. 124.7 ± 25.6 mmHg, p < 0.0001). LVET was significantly associated with CMD (1.42 [1.02–1.96], p = 0.04), while a non-statistically significant link was observed for A-wave velocity and E/E′-ratio (1.39 [0.96–2.00], p = 0.08 and 1.40 [0.92–2.13], p = 0.1, respectively). For all other echocardiography-derived measures, odds ratio for the association with CMD was <1.3 per each SD increase.
Conclusions: In this cross-sectional single-center cohort study, CMD was a frequent finding in patients undergoing coronary angiography for suspected obstructive coronary artery disease. LVET from transthoracic echocardiography is associated with the presence of CMD.

1. Introduction

Coronary microvascular dysfunction (CMD) is a heart disease that affects the walls and inner lining of small coronary artery blood vessels that branch off from the larger coronary arteries [1]. It is defined as impaired coronary blood flow in the absence of myocardial diseases. CMD frequently causes similar clinical symptoms as obstructive coronary artery disease. While symptoms and risk factors like aging, hypertension, diabetes, and dyslipidemia are similar

to obstructive coronary artery disease, diagnosing CMD is challenging [2–5]. Left ventricular end-diastolic pressure (LVEDP) is correlated with presence of CMD and, therefore, commonly used for its diagnosis [6,7]. The gold standard method for assessing ventricular filling pressure is the measurement of the LVEDP during cardiac catheterization [8]. Accordingly, non-invasive estimation of LVEDP is an important goal in the evaluation of CMD. While positron emission tomography (PET) and magnetic resonance imaging (MRI) allow for the assessment of absolute myocardial blood flow and flow reserve [9], these do not qualify for routine testing due to limited availability even in industrialized countries. However, as echocardiography is broadly available and allows for the assessment of ventricular filling pressures, it could serve as a first diagnostic tool for the diagnosis of potential CMD.

The aim of this study was to determine whether echocardiographic measures of left ventricular diastolic function, filling pres-

* Corresponding author at: Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center Essen, University Hospital Essen, Hufelandstr. 55, 45147 Essen, Germany.

E-mail address: Iryna.dykun@uk-essen.de (I. Dykun).

[1] All author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

sure, and hypertrophy may predict the presence of CMD, and to assess whether echocardiography qualifies as a screening test for CMD.

2. Methods

2.1. Study subjects

We retrospectively included consecutive patients undergoing diagnostic coronary angiography for suspected coronary artery disease as well as transthoracic echocardiography between March and October 2016 at our center. Patients with obstructive coronary artery disease, previous revascularization therapy, moderate or severe mitral valve disease, or atrial fibrillation were not included. CMD was defined as left-ventricular end-diastolic pressure (LVEDP) ≥15 mmHg, presence of hypertensive heart disease, or relevant slow flow (TIMI flow ≤II). Cholesterol levels, demographic characteristics, cardiovascular risk factors (systolic and diastolic blood pressure, smoking status, positive family history of premature coronary artery disease manifestation, BMI), blood test results, and medical therapy were assessed from available patient records. The analysis was approved by the local ethics committee (18-8177-BO) without the need of informed consent from the included patients, given the retrospective nature of the data with anonymous data assessment.

2.2. Echocardiographic measurements

Echocardiography was performed using an Epiq 7C system with an X5-1 probe (Philips Medical Systems, Eindhoven, The Netherlands), or a Vivid E9 system with an M5S-D probe (GE Healthcare, Buckinghamshire, UK). The following markers of left ventricular diastolic function and hypertrophy were assessed from transthoracic echocardiography: E-, A-, E-wave deceleration time, E/A- and E/E'-ratio, mitral valve closure to opening time (MCOT), and LVET.

The LV end-diastolic dimension and the thicknesses of the interventricular septum and LV-posterior wall were measured in the end-diastolic parasternal long axis images at the chordal level in M-mode wherever possible (when septal and posterior wall were horizontal to the m-mode, alternatively in 2D echocardiographic) according to the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) Recommendations and LV mass was calculated accordingly [10]. Finally, the LV mass was corrected for each patient́s body surface area (BSA) according to the DuBois formula. The left atrial (LA) area was measured from apical four chamber view at the end systole, shortly before the mitral valve opens.

With standard transthoracic pulsed wave (PW)-Doppler echocardiography using the apical four chamber view, the peak early-diastolic (E), atrial systolic (A) transmitral flow velocities, the deceleration time of the E wave (DT), and the mitral valve closure to opening time (MCOT) were measured, according to the ESE/EACVI recommendations for the evaluation of left ventricular diastolic function [11]. Left ventricular ejection time (LVET) was assessed with pulsed-Doppler echocardiography of the left ventricular outflow tract in the apical five-chamber view. In addition, the velocity of mitral annular motion at the lateral ring (Lateral E) using PW tissue Doppler was measured.

2.3. Left heart catheterization

Left heart catheterization was performed in the supine position using 5F or 6F catheters via the retrograde approach from a femoral or radial artery. In all procedures, a pigtail catheter was used for crossing of the aortic valve. Left ventricular peak pressure and LVEDP were measured at rest in a steady state. The LVEDP was measured during expiration at end-diastole, which was defined by the onset of the next QRS cycle wave on ECG from left pressure tracing, recorded with a 200 mmHg scale. Standard diagnostic views of the left and right coronary anatomy were obtained, and lesions ≥70% by diameter in major epicadial arteries represented significant coronary artery disease (≥50% for left main). For the blood flow assessment, the Thrombolysis in Myocardial Infarction (TIMI) frame out was used [12]. The presence of hypertensive heart disease was defined as tortuosity of the coronary arteries, as by judgement of experienced invasive cardiologists. Reading of invasive cardiac hemodynamics and coronary anatomy were performed by experienced invasive cardiologists.

2.4. Statistical analysis

The baseline characteristics are presented as mean ± standard deviation for continuous variables and as frequency and percentages for categorical variables and stratified by presence and absence of CMD. Due to its skewed distribution, for NT-pro BNP median and IQR were depicted. Two-sided *t*-test was used for normally distributed continuous variables, Wilcoxon rank-sum tests for non-normally distributed continuous variables, and Fisher's Exact test or Chi-square test for categorical variables. Logistic regression analysis was used to determine the association of echocardiographic parameters with presence of CMD using the following models: (a) unadjusted, (b) age, sex, systolic blood pressure, LDL-cholesterol, and diabetes adjusted as known predictors of CMD. Given the overall number of patients with and without CMD, overfitting was not of concern. In addition, the authors tested for co-linearity of all included variables in the multivariable model and again observed no restrictions. Effect sizes were depicted per each standard deviation change in echocardiographic measure. Receiver operating characteristic (ROC) curve analysis was used to compare the performance of echocardiographic parameters in predicting CMD over age, sex, systolic blood pressure, LDL-cholesterol, and diabetes. All analyses were performed using SAS software (Version 9.2, SAS Institute Inc.). A p-value of <0.05 was considered to indicate statistical significance.

3. Results

Overall, 379 patients (mean age 59.7 ± 13.6 years, 45.6% male) undergoing diagnostic coronary angiography for suspected coronary artery disease as well as transthoracic echocardiography between March and October 2016 were included. CMD was present in the majority of patients (n = 293, 77.5%). The mean ± SD LVEDP was 14.7 ± 7.8 mmHg, TIMI flow <2 was present in 11 patients, and 178 presented with signs of hypertensive heart disease (tortuosity of the coronary arteries, as by judgement of the experienced invasive cardiologists) in cardiac catheterization. The clinical parameters are summarized in Table 1. Patients without CMD were younger (56.9 ± 14.3 years vs. 60.5 ± 13.4 years, two-sided *t*-test p = 0.03), were more frequently male (male: 57.0% vs. 42.3%, p = 0.02), and had lower systolic blood pressure (124.7 ± 25.6 mmHg vs. 137.9 ± 25.7 mmHg, p < 0.0001, for patients without and with CMD, respectively). In contrast, BMI, presence of diabetes mellitus, cholesterol levels, NT-pro BNP, and glomerular filtration rate were not statistically different between patients with and without CAD (p > 0.05 for all). As for medication use, there were no statistically significant differences between the two groups, except of cholesterol-lowering medication, which was less frequent in patients without CMD (6.6% vs 32.2%, p = 0.03). Overall, 35.6% of the patients had LV hypertrophy.

All Doppler and echocardiography parameters, stratified by presence and absence of CMD, are summarized in Table 2. Compar-

Table 1
Baseline characteristics in all patients and stratified according to CMD.

Variable	All patients (n = 378)	Patients with CMD (n = 293)	Patients without CMD (n = 85)	p-value
Age, years	59.7 ± 13.6	60.5 ± 13.4	56.9 ± 14.3	0.03
Gender, male	171 (45.6)	123 (42.3)	48 (57.0)	0.02
BMI, kg/m^2	27.6 ± 5.8	27.8 ± 6.0	26.6 ± 5.2	0.1
Diabetes melitus, n (%)	57 (15.5)	46 (12.5)	11 (3.0)	0.5
Family history of CAD, n (%)	67 (18.3)	56 (15.3)	11 (3.0)	0.2
Current smoker, n (%)	59 (16.1)	47 (12.8)	12 (3.3)	0.6
Total Cholesterol, mg/dl	195.7 ± 49.7	194.2 ± 52.1	201.0 ± 40.3	0.3
HDL-cholesterol, mg/dl	54.8 ± 17.4	54.9 ± 18.0	54.7 ± 15.7	0.9
LDL-cholesterol, mg/dl	126.1 ± 40.4	125.3 ± 41.8	128.8 ± 35.4	0.6
Triglyceride, mg/dl	143.7 ± 89.5	141.8 ± 86.8	150.5 ± 99.0	0.5
NT-pro BNP (median [Q1;Q3]), pg/ml	147 [57;499]	153 [55;498]	108 [65;678]	0.7
Systolic blood pressure, mmHg	134.9 ± 26.2	137.9 ± 25.7	124.7 ± 25.6	<0.0001
Diastolic blood pressure, mmHg	68.1 ± 13.4	69.5 ± 13.3	63.6 ± 12.7	0.0003
Cholesterol-lowering therapy, n (%)	141 (38.8)	117 (32.2)	24 (6.6)	0.03
ACE/ARB, n (%)	213 (58.7)	171 (47.1)	42 (11.6)	0.09
ß -Blockers, n (%)	239 (65.8)	185 (50.1)	54 (14.9)	0.9
Calcium channel blocker, n (%)	89 (24.5)	72 (19.8)	17 (4.7)	0.3
Diuretics, n (%)	160 (44.1)	128 (35.3)	32(8.8)	0.2
LVEDP, mmHg	14.7 ± 7.8	16.5 ± 7.6	8.5 ± 4.5	<0.0001

SD: standard deviation; CMD: coronary microvascular dysfunction; BMI: body mass index; CAD: cardiac artery disease; HDL: high density lipoprotein; LDL: low density lipoprotein; NT-pro BNP: N-terminal pro-brain natriuretic peptide; ACE/ARB: angiotensin-converting-enzyme inhibitors/ a Angiotensin II receptor blockers.

ing echocardiographic measures between patients with and without CMD, we observed that peak A-wave velocity and LVET were higher in patients with CMD (75.8 ± 25.6 cm/s vs. 68.9 ± 23.3 cm/s, p = 0.03 for peak A-wave velocity and 309.0 ± 41.6 ms vs. 291.7 ± 54.4 ms, p = 0.01 for LVET, Fig. 1). A non-statistically significant association was observed the link of E/E′ ratio with CMD (8.4 ± 4.0 vs 7.6 ± 3.5, p = 0.1).

In unadjusted regression analysis, LVET was significantly associated with presence of CMD (Table 3). The effect was persevered when adjusting for age, sex, and systolic blood pressure as variables significantly different between patients with and without CMD. Likewise, the A-wave velocity was significantly associated with presence of CMD. However, the effect was attenuated when adjusting for age, sex, and systolic blood pressure. For E/E′-ratio, relevant effect sizes were observed, but were not statistically significant. For all other echocardiography derived measures, odds ratio for the association with CMD was <1.3 per each SD increase (Table 3).

In receiver operating characteristic curve analysis, adding A-wave velocity to age, sex, systolic blood pressure, LDL-cholesterol, and diabetes only modestly improved the area under the curve (ROC = 0.729 [0.648–0.809] for age, sex, systolic blood pressure, LDL-cholesterol, and diabetes, ROC = 0.725 [0.662–0.823] ancillary for A-wave velocity, p = 0.33). Likewise, adding LVET to age, sex, systolic blood pressure, LDL-cholesterol, and diabetes only modestly improved the AUC to 0.751 [0.674–0.833] (p = 0.22 for difference). Combining the information from A-wave velocity and LVET complementary improved the area under the ROC curve, however, not reaching statistical significance (ROC = 0.729 [0.648–0.809] for age, gender, systolic blood pressure, LDL-cholesterol, and diabetes, ROC = 0.760 [0.682–0.838], ancillary for A-wave velocity and LVET, p = 0.15; Fig. 2).

4. Discussion

In the present study, we evaluated whether transthoracic echocardiography derived measures of left ventricular diastolic function and hypertrophy could predict presence of CMD and whether echocardiography qualifies as a screening test for CMD. Ultimately, the goal of the study was to assess, if echocardiography qualifies as a screening test for CMD. Overall, we observed that CMD is a frequent finding in our patients undergoing coronary angiography without detection of obstructive coronary artery disease. Among all echocardiographic parameters, the A-wave veloc-

ity and the LVET were significantly associated with the presence of CMD, while a non-statistically significant association was observed for E/E′ ratio. However, despite their complemental value, echocardiographic measures only marginally improved the prediction of CMD. Our data suggest that routinely assessed measures of left ventricular diastolic function and hypertrophy from transthoracic echocardiography alone may not qualify as reliable screening tools for CMD.

Over the last few years, several studies on Doppler echocardiography to non-invasively estimate intracardiac pressures have been performed [7,13–16]. Focusing on LVEDP, a recent study found that echocardiographic estimates of left ventricular filling pressure and diastolic function (E/A Ration, E/E′ Ratio and LA volume) were marginally correlated with LVEDP [17]. In a cohort of 159 patients (53% with presence of obstructive coronary artery disease), the Euro-Filing study demonstrated that even the latest recommendations for the non-invasive assessment of LVEP could only moderately identify patients with elevated LVEDP (≥15 mmHg) with a sensitivity of 43%, a specificity of 75%, and positive predictive value of 49% [18]. In the present study on 379 patients without obstructive coronary artery disease, we found that E/A ratio and LA area were only marginally higher in patients with CMD.

It is well known that in hypertensive patients, left ventricular workload is increased, resulting in LV hypertrophy, impaired left ventricular relaxation, and left atrial enlargement [19]. LV hypertrophy is associated with both echocardiographic measures of diastolic function and presence of CMD [20–22]. However, in the present study, we observed no significant association of LV mass index as measure of LV hypertrophy with presence of CMD. This could be explained by early hemodynamic changes in the left ventricle, leading to CMD before the occurrence of LVH.

In clinical routine, CMD is a frequent disease, leading to myocardial ischemia. Due to identical common final path, clinical symptoms are similar to obstructive coronary artery disease. Therefore, patients with CMD frequently receive coronary angiography examinations for suspected obstructive coronary artery disease. Indeed, in our consecutive cohort, CMD was present in the majority of patients without obstructive CAD. Therefore, there is a clinical need for alternative non-invasive testing, allowing for reliable screening of CMD.

Taken together, our results suggest that the A-wave velocity and LVET are associated with the presence of CMD; however, measures

Table 2
Doppler and echocardiography measurements in all patients and stratified according to CMD.

Variable	All patients (n = 378)	Patients with CMD (n = 293)	Patients without CMD (n = 85)	p-value
Peak E-wave velocity, cm/s	75.9 ± 23.6	76.7 ± 24.0	72.9 ± 21.7	0.2
Peak A-wave velocity, cm/s	74.2 ± 25.2	75.8 ± 25.6	68.9 ± 23.3	0.03
E Deceleration time, ms	181.7 ± 75.2	183.8 ± 74.1	174.5 ± 78.9	0.3
E/E' Ratio	8.2 ± 3.9	8.4 ± 4.0	7.6 ± 3.5	0.1
E/A Ratio	1.2 ± 0.68	1.16 ± 0.7	1.2 ± 0.6	0.7
MCOT, ms	403.3 ± 67.1	405.4 ± 70.5	396.2 ± 53.7	0.2
LVET, ms	305.2 ± 45.3	309.0 ± 41.6	291.7 ± 54.4	0.01
LA area, cm^2	20.1 ± 7.2	20.2 ± 7.6	19.4 ± 5.4	0.3
LV mass index (g/m^2)	100.9 ± 36.4	101.6 ± 37.8	98.7 ± 31.6	0.5

CMD: coronary microvascular dysfunction; MCOT: mitral valve closure to opening time; LVET: Left ventricular ejection time; LA: left atrial; LV: left vetricular.
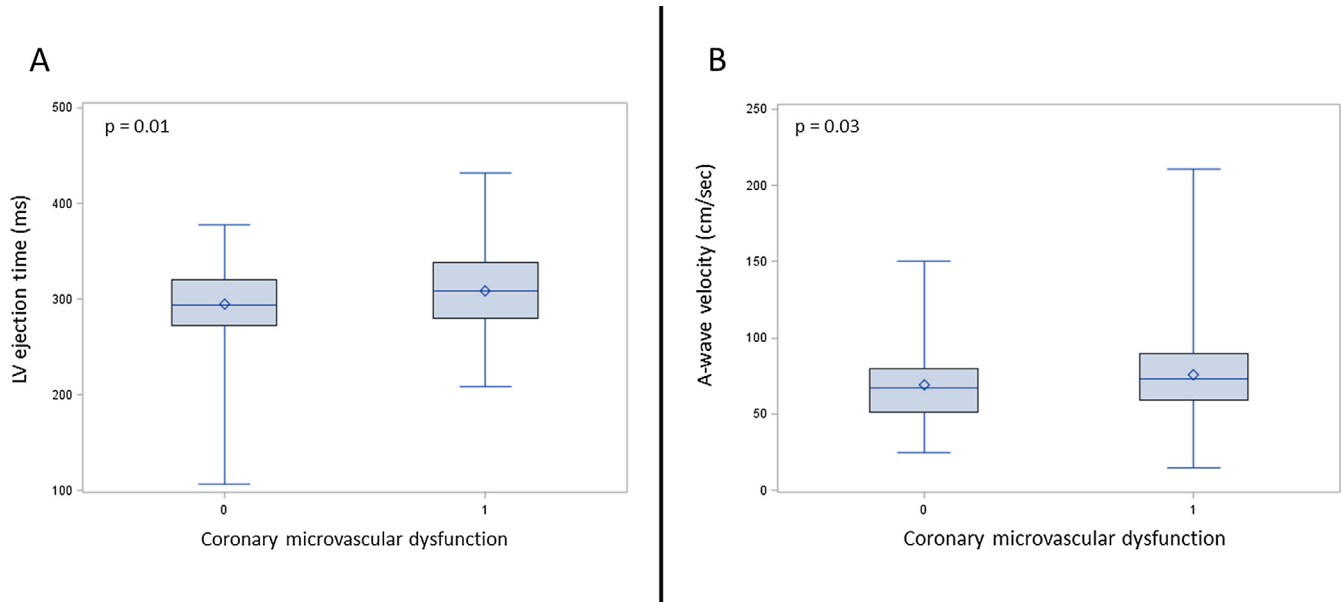

Fig. 1. Boxplot for the differences in LV ejection (A) time and A-wave velocity (B) between patients with and without coronary microvascular dysfunction. The Boxplots represent median and interquartile range, while the error bars depict the 2.5th and 97.5th percentile. Statistical significance between patients with CMD (n = 293) and without CMD (85) are assessed using a 2-sided t-test.

Table 3
Univariable and multivariable logistic regression analysis for the prediction of CMD. Effect sizes are depicted per each standard deviation of echo measure.

	Unadjusted OR (95%CI)	p-value	Adjusted* OR (95%CI)	p-value
Peak E-wave velocity	1.19 [0.92–1.52]	0.2	1.25 [0.95–1.65]	0.1
Peak A-wave velocity	1.34 [1.03–1.75]	0.028	1.39 [0.96–2.00]	0.08
E Deceleration time	1.13 [0.89–1.45]	0.3	1.22 [0.87–1.72]	0.3
E/E' Ratio	1.26 [0.95–1.68]	0.1	1.40 [0.92–2.13]	0.1
E/A Ratio	0.96 [0.76–1.21]	0.7	0.99 [0.70–1.39]	0.9
MCOT	1.15 [0.9–1.47]	0.3	1.00 [0.73–1.38]	1.0
LVET	1.46 [1.14–1.87]	0.003	1.42 [1.02–1.96]	0.03
LA area	1.13 [0.87–1.48]	0.4	1.13 [0.74–1.73]	0.6
LV mass index	1.09 [0.84–1.40]	0.5	1.10 [0.77–1.57]	0.6

CMD: coronary microvascular dysfunction; MCOT: mitral valve closure to opening time; LVET: Left ventricular ejection time; LA: left atrial; LV: left vetricular.
* Adjusted for age, gender, sys RR, LDL-cholesterol, and diabetes.

of diastolic function and LV hypertrophy alone from transthoracic echocardiography did not improve its prediction. There is a need for further studies evaluating how non-invasive measurements – including multimodal imaging – in addition to quantification of A-wave velocity and LVET from echocardiography can improve the screening of different coronary artery disease entities [23–26].

5. Limitations

There are several limitations of this study. First, our results are based on a retrospective cohort. Given its cross-sectional design,

we cannot establish causality. Most importantly, we did not assess coronary flow reserve for assessment of CMD, as these are not routinely available in clinical practice. Instead, we used increased left ventricular end-diastolic pressure, coronary slow flow, and hypertensive heart disease as surrogate markers, which are available on every routine coronary angiography. Further, we were limited by the relatively low frequency of patients without CMD in our cohort. Lastly, we excluded patients without synchronized atrial activity due to arrhythmias such as atrial fibrillation, atrial flutter, and complete atrioventricular block as key measures of diastolic function depend on a synchronized atrial contraction.
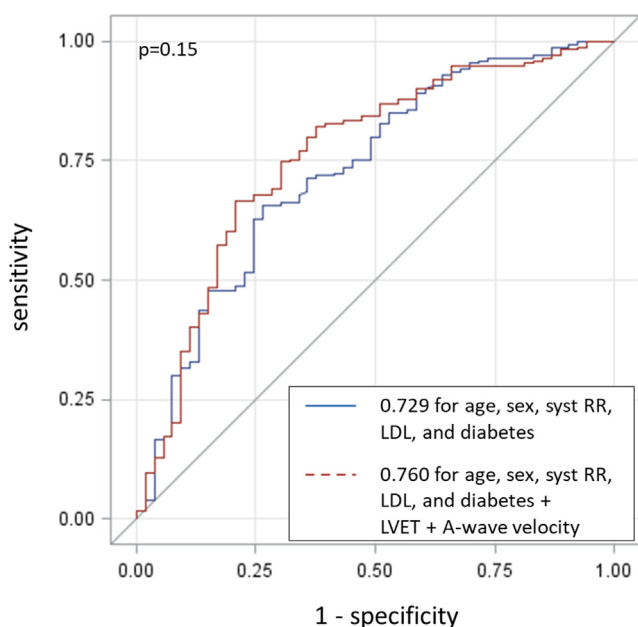
Fig. 2. Receiver operating characteristic curve analysis for the improvement in prediction of CMD by A-wave velocity and LVET over age, sex, systolic blood pressure, LDL-cholesterol, and diabetes.

6. Conclusions

In this cross-sectional single-center cohort study, CMD is a frequent finding in patients undergoing coronary angiography for suspected obstructive coronary artery disease. A-wave velocity and LVET, as quantified from transthoracic echocardiography, are associated with the presence of CMD, but do not qualify for CMD prediction. Further research is warranted to determine additional non-invasive predictors to help improve the pretest-probability and ultimately avoid unnecessary invasive testing.

CRediT authorship contribution statement

Iryna Dykun: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft. **Luisa Kärner:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Ihab Mahmoud:** Investigation, Writing - review & editing. **Stefanie Hendricks:** Investigation, Writing - review & editing. **Matthias Totzeck:** Resources, Writing - review & editing. **Fadi Al-Rashid:** Resources, Writing - review & editing. **Tienush Rassaf:** Funding acquisition, Supervision, Writing - review & editing. **Amir A. Mahabadi:** Conceptualization, Supervision, Writing - review & editing.

Acknowledgements

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