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Coronary microvascular dysfunction is associated with cardiac time intervals in women with angina and no obstructive coronary artery disease: an iPOWER substudy

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ABSTRACT

Background

Coronary microvascular dysfunction (CMD) may cause angina in absence of obstructive coronary artery disease (CAD) and increases the risk of future adverse cardiovascular events. Transthoracic Doppler echocardiography (TTDE) with pharmacological stress can assess coronary flow velocity reserve (CFVR), a measure of coronary microvascular function. However, simpler methods would be preferable for diagnosing CMD. Therefore, we examined the relationship between CFVR and cardiac time intervals measured by TTDE in a cohort of women with angina and no obstructive CAD.

Methods

In a prospective cohort study, we included 389 women with angina, left ventricular ejection fraction >45% and no obstructive CAD. CMD was defined as CFVR<2.0. The study population was divided into three groups according to cut-off values of CFVR<2, 2≤CFVR≤2.5 and CFVR>2.5. Isovolumic contraction time (IVCT), ejection time (ET) and isovolumic relaxation time (IVRT) were measured by tissue Doppler M-mode and the myocardial performance index (MPI = (IVCT+IVRT)/ET) was calculated.

Results

CMD was associated with increasing age, hypertension, higher resting heart rate and lower diastolic blood pressure. Moreover, CMD was associated with higher E/e′-ratio (p=0.002) and longer IVCT (p<0.001), higher MPI (p<0.001) and shorter ET (p=0.002), but not with IVRT or conventional measures of left ventricular geometry, mass and function. In multivariable analysis longer IVCT (p<0.001) and higher MPI (p=0.002) remained associated with CMD.
**Conclusion**
In women with angina and no obstructive CAD, CMD is associated with longer IVCT and higher MPI indicating a link between CMD and subtle alternations of systolic and combined measures of cardiac time intervals.

**Keywords**
Coronary flow reserve, myocardial performance index.

**INTRODUCTION**
Coronary microvascular dysfunction (CMD) is increasingly recognized as a cause of angina pectoris (AP) in patients without obstructive coronary artery disease (CAD)\(^1\). CMD can be assessed non-invasively by transthoracic Doppler echocardiography (TTDE) with pharmacological stress as a significant reduction of the coronary flow velocity reserve (CFVR) in a major epicardial coronary artery (usually the left anterior descending artery [LAD])\(^2\), and low CFVR has been shown to be an independent marker of adverse prognosis in a variety of patient subgroups, including in patients with AP without obstructive CAD\(^3-5\).

In patients with suspected stable CAD, guidelines recommend a resting echocardiography as part of the initial test program\(^6\). At present, obstructive CAD is ruled out by functional and anatomical testing and detection of CMD requires additional tests. Therefore, evaluation of the capacity of parameters that are easily obtained during the guideline-recommended standard resting TTDE to predict CMD in absence of obstructive CAD is warranted. Tissue Doppler imaging (TDI) with recording of mitral annular velocities is an integrated part of the standard echocardiographic examination, mainly for providing information on early diastolic peak velocity (e’) that is used for evaluation of left ventricular (LV) diastolic function\(^7\). However, if recorded at sufficiently high frame rates, TDI loops can be analyzed for a variety of other parameters, including cardiac time intervals from which the myocardial performance index (MPI) can be calculated. MPI incorporates both systolic and diastolic time intervals and predicts both major cardiovascular events and overall mortality in a general population free of cardiovascular risk factors\(^8,9\) as well as in patients with ST-segment elevation myocardial infarction\(^10\).

The potential for assessment of CMD by conventional TDI echocardiography in women with AP and no obstructive CAD has not been explored previously and it is plausible that MPI is impaired.
in patients with CMD. Therefore, we hypothesized that in these women, MPI was associated with CFVR assessed by TTDE.

METHODS

Population

From the previously described prospective iPOWER (imPrOving diagnosis and treatment of Wome$n$ with angina pEctoris and microvasculaR disease) cohort\(^\text{11}\) we included participants who between March 1\(^{\text{st}}\) 2013 and June 18\(^{\text{th}}\) 2014 had high frame rate TDI acquisition performed by 2 experienced echocardiographers (AP and MM). Participants in the iPOWER cohort were women 18-80 years of age referred for a clinically indicated diagnostic invasive coronary angiography (CAG) due to angina-like chest pain that were found to have no obstructive CAD (<50% stenosis), LVEF >45% and no significant valvulopathy. In this substudy, additional exclusion criteria were the presence of atrial fibrillation, pacemaker, left or right bundle branch block on the ECG and unsuccessful measurement of CFVR.

Baseline data

Baseline data included cardiovascular risk factors, i.e. age, body mass index (BMI), diabetes, hypertension, hypercholesterolemia, smoking, and family history of ischemic heart disease. Blood pressure and heart rate were obtained at rest.

Echocardiography

Participants underwent a standard resting TTDE using GE Healthcare Vivid E9 cardiovascular ultrasound system (GE Healthcare, Horten, Norway) with a 1.3-4.0 MHz transducer (GE Vivid 5S probe). Images were stored for off-line analysis (GE EchoPAC v.112, Norway). TDI loops focusing on the LV were obtained in the apical long axis, 2- and 4-chamber at a high frame rate (166-200 frames/sec). One experienced echocardiographer (AP) blinded to the CFVR results performed the TDI analysis. All values were averaged over 3 consecutive cycles, however, in case of LV pendulation due to respiration, only values from the most stable loop were used.

CFVR measurement

Participants underwent a TTDE of the LAD during rest and high-dose dipyridamole stress (0.84 mg/kg over 6 minutes) to obtain coronary flow velocity (CFV) at rest and during maximal
hyperemia using a 2.7-8 MHz transducer (GE Vivid 6S probe). Two experienced
echocardiographers performed all examinations in the same setting. Participants were instructed to
abstain from caffeine or food containing significant amount of methylexanthine (coffee, tea,
chocolate, cola and banana) for 24 hours. Abstinence was confirmed by the interviewer.
Medication containing dipyridamole was paused for 48 hours, long-lasting nitro-glycerine, anti-
hypertensive and anti-ischemic medication for 24 hours and short-lasting nitro-glycerine for 1 hour
before the examination. Patients were examined in the left lateral decubitus position. The octave
was set at 3.1/6.2 MHz, frequency at 8MHz for B-mode (2D) and a baseline color scale at 1.00–
2.50 KHz (velocity range ± 10–24 cm/sec) according to low or high flow velocities. Color gain was
adjusted to provide optimal 2D imaging quality. Depending on viewing window, the LAD was
visualized by color Doppler in a modified apical foreshortened 2-, 4-chamber or a modified short-
axis view of the left ventricle. CFV was measured by pulse wave (PW) Doppler as a laminar flow
towards the transducer. We aimed to align the direction of the ultrasound beam to that of the LAD
flow by adjusting probe position. The direction was kept during recording of 2D and PW images. If
visualization of the LAD was difficult, a micro bubble contrast agent was used (SonoVue®, Bracco
Imaging). CFV during dipyridamole infusion were acquired throughout the 6-minute infusion and
up to 3 minutes hereafter, until flow had reached a stable peak velocity. Blood pressure and heart
rate were measured every 3 minutes during the dipyridamole infusion. Intravenous theophylline
(maximum dose 220 mg) was administered at the end of the examination if necessary to relieve
potential side effects of dipyridamole.

CFVR values defined as peak diastolic CFV during maximal hyperemia/CFV during rest were
analysed by two experts, blinded to patient data, independently. The first of the two readings was
used when estimates differed by less than 0.2; otherwise the CFVR was re-examined and an
agreement was reached between both echocardiographers. For CFVR measurements we have
previously reported an inter-reader coefficient of variation (COV) of 2.9%\textsuperscript{11}, and reliability of
measurements was high with an intraclass correlation coefficient of 97% in healthy young subject
and of 90% in women from the iPOWER cohort\textsuperscript{12}.

Left ventricular ejection fraction, dimensions and diastolic parameters
LVEF was analysed as a semi-automated biplane calculation at rest (Auto-EF tool, GE EchoPAC
v.112, Norway). LV internal dimension at diastole (LVIDd), posterior wall thickness at diastole
(PWTd), septum wall thickness at diastole (SWTd) and LV internal diameter at systole (LVIDs) were analyzed in a 2D parasternal long-axis image according to recommendations\textsuperscript{13}. LV mass was calculated \( ((0.8 \times (1.04 \times [(LVIDd + PWTd + SWTd)^3 – (LVIDd)^3]) + 0.6 \text{ g})) \) and indexed for body surface area calculated by Du Bois’ formula to obtain LV mass index (LVMI)\textsuperscript{14}. Left atrium (LA) volume was measured in the apical 2- and 4-chamber view in end systole just before mitral valve opening by the ‘Volume Method of Discs’ (GE EchoPac v.112, Norway), and the volumes were averaged. LA volume was indexed (LAVI) by dividing LA volume by body surface area. PW Doppler imaging was performed using a 3-mm sample volume placed between the mitral leaflet tips in the apical 4-chamber view to obtain peak early filling velocity (E) and deceleration time (DT). PW tissue Doppler was used to measure early (e’) diastolic velocity in the septal and lateral corners of the mitral ring and E/e’ ratios were calculated. In case of fusion between e’ and a’, values were listed as missing.

Cardiac time intervals
The cardiac time intervals were calculated using timing events sampled from a single apical 4-chamber TDI view. An approximately 4 cm straight curved anatomical M-mode line was placed through the anterior mitral leaflet, and the timing events were measured directly from the color diagram (Figure 1). Mitral valve closure (MVC) was defined as the color shift from blue/turquoise to red at end diastole. Aortic valve opening (AVO) was defined as the following color shift from blue to red at the start of systole. Aortic valve closure (AVC) was defined as the following color shift from red to blue at end systole. Mitral valve opening (MVO) was defined as the color shift from red/orange to yellow before the start of diastole. The isovolumic contraction time (IVCT = AVO - MVC), isovolumic relaxation time (IVRT = MVO - AVC), ejection time (ET = AVC - AVO) and myocardial performance index (MPI = [IVCT + IVRT] / ET) were calculated.

Mitral annular velocities
Mitral annular velocities were measured within a sample volume measuring 3x6 mm placed in the mitral annulus with the loop stopped in the AVC in the lateral and septal mitral annular positions and averaged to obtain systolic (s’), early diastolic (e’), and late diastolic (a’) velocities. If no visible pendulation of LV was observed a visual average of all three loops was used.

Statistical analyses
All continuous variables with a Gaussian distribution are expressed as means ± standard deviations (SDs). Counts in % was used for categorical variables. Normal distributions were assessed graphically.
The study population was divided into three groups according to cut-off values of CFVR <2, 2≤ CFVR ≤2.5 and CFVR >2.5, respectively. Associations between CFVR groups, cardiovascular risk factors and echocardiographic parameters were investigated by trend test (linear regression or logistic regression) in univariable analysis, and as linear regression using CFVR as a continuous variable when performing multivariable analysis. In the multivariable model we adjusted for predefined risk factors known to influence CFVR (age, hypertension, diabetes mellitus, current smoking and resting heart rate) as previously described. Variability and repeatability of MPI analysis was assessed by the Bland-Altman method, and agreement expressed as COV (%) calculated by dividing the SD for the difference between measurements with the mean MPI.

CMD was defined as CFVR <2.0. The corresponding optimal cut-off value for MPI to identify CMD was assessed by receiver operating characteristics (ROC).

Confidence intervals (CIs) refer to 95% intervals and a two-sided p-value below 0.05 was considered significant. All analyses were performed using STATA/IC 13.1 (StataCorp LP, College Station, TX, USA).

Ethics
This study was performed in accordance with the Helsinki Declaration and was approved by the Danish Regional Committee on Biomedical Research Ethics (H-3-2012-005). All patients gave written informed consent, after receiving oral and written information about the study.

RESULTS
Study population
A total of 615 participants were included in the study period. Participants examined without high frame rate TDI acquisition (n=163), with atrial fibrillation (n=9), without a successful CFVR measurement (n=20), with either right or left bundle branch block (n=33) and with a pacemaker (n=1) were excluded. Hence, 389 participants were eligible for the final analysis, and cardiac time intervals were successfully measured in all of these. e’ and a’ were successfully measured in 384 participants, whereas s’ was successfully measured in 388 participants.
Association between cardiovascular risk factors, conventional echocardiographic parameters, medication and CFVR

Table 1 shows clinical characteristics, conventional echocardiographic measures and relevant cardiovascular medications in the three groups of CFVR by predefined cut-off values as described above. Notably, 119 (30.6%) women had CMD defined as a CFVR <2. Lower CFVR was associated with older age, hypertension, increased resting heart rate, lower diastolic blood pressure and increased E/e' -ratio. No difference in consumption of common antihypertensive drugs, long acting nitroglycerins, statins or acetylsalicylic acid was found. Adjustment for age did not alter these results albeit that current smoking became significantly associated with lower CFVR (p for trend=0.025). In multivariable linear regression analysis adjusting for age, hypertension, diabetes mellitus, current smoking and resting heart rate, the significant association between lower CFVR and E/e' disappeared.

Association between TDI parameters, cardiac time intervals and CFVR

Table 2 shows mitral annular velocities and cardiac time intervals across the three CFVR groups. Mean s' was 5.9 (0.9) cm/s, e' -7.0 (1.8) cm/s, a' -7.2 (1.4) cm/s, IVCT 32.8 (11.4) ms, IVRT 99.2 (16.4) ms, ET 298.1 (26.3) ms and MPI 0.45 (0.08). Lower CFVR was associated with higher IVCT, shorter ET and a higher MPI. In the multivariable analysis adjusting for age, hypertension, diabetes mellitus, current smoking and resting heart rate, IVCT (Figure 2) and MPI (Figure 3) remained the only parameters significantly associated with CFVR as a continuous variable although the explanatory values of the models were low ($r^2=0.16$ and $r^2=0.12$, respectively). Using CFVR as a binary classifier with 2.0 as the cut-off value for CMD the optimal cut-off value for MPI was estimated to be 0.43. However, sensitivity and specificity were only 0.66 and 0.53, respectively. The associated area under the ROC curve was 0.61.

Reproducibility of MPI

To test the reproducibility of MPI measurements, intra- and inter-reader results in 20 participants as well as intra-reader analyses of repeat MPI examinations in 10 healthy controls were assessed. COV for intra- and inter-reader analyses were 5.5% and 9.4% respectively, while the COV for intra-reader analyses for repeat examination was 12.9% (Figure 4).
DISCUSSION

In the current study of women with AP and no obstructive CAD, we found that CMD defined as CFVR <2.0 by dipyridamole stress TTDE was associated with higher E/e’, longer IVCT, higher MPI and lower ET, respectively, but not with IVRT, mitral annular velocities or other conventional echocardiographic measures. After multivariable adjusting, only IVCT and MPI remained associated with CFVR.

Associations between conventional echocardiographic parameters, mitral annular velocities and CFVR

In clinical practice estimation of LV systolic function is essential for risk assessment in patients with known or suspected cardiac disease, and LVEF is the most widely used echocardiographic parameter to identify patients at risk of major adverse cardiovascular outcomes. Low or declining values over time modulate risk assessment and treatment strategies in a range of patient groups, including patients with heart failure\textsuperscript{15}, and aortic valve disease with stenosis or regurgitation\textsuperscript{16}, respectively. In subjects with preserved LVEF and no significant valve disease, other echocardiographic parameters such as e’, E/A, E/e’ and LV mass identify individuals with increased risk of morbidity and mortality in the general population\textsuperscript{17–19}, and their use in assessment of LV diastolic function has been established\textsuperscript{20}. We therefore evaluated the association of these easily obtained resting parameters during the guideline recommended echocardiography with reduced CFVR by TTDE with pharmacological stress. In univariable analysis we found an association between E/e’-ratio, an estimate of LV filling pressure, and CMD but in multivariable analysis this association disappeared. No other echocardiographic parameters including mitral annular velocities, E/A ratio, DT, LVMI or LAVI were associated with CFVR in univariable analysis. A recent study investigated 201 patients (64.7% women) with normal LVEF, no significant valve disease and no flow-limiting CAD at stress cardiac positron emission tomography (PET)\textsuperscript{21}. Coronary flow reserve (CFR) was derived from the PET examination and when examined for associations with measures of diastolic function, only septal E/e’ remained associated with CFR in multivariable analysis. The combination of CFR<2 and E/e’>15 was the strongest predictor of subsequent hospitalization for heart failure with preserved ejection fraction. Similar results have been found in patients with angina free from heart failure, with no obstructive CAD and no significant valve disease (n=73)\textsuperscript{22}, with type 2 diabetes (n=67)\textsuperscript{23} and in patients with newly diagnosed hypertension (n=59)\textsuperscript{24}. A link between CFVR and e’ or LVMI was not consistently found in these studies and no association between LAVI or a’ was reported\textsuperscript{22–24}.
**Associations between cardiac time intervals and CFVR**

MPI is an integrated measure of the combined systolic and diastolic function of the myocardium and can be calculated by conventional PW Doppler tracings of mitral inflow and LV outflow or by color TDI M-mode identification of characteristic color shifts that identify the opening and closing of valves used to calculate the cardiac time intervals as utilized in the present study. Although absolute values vary between these methods, they show a strong correlation with each other. MPI by color TDI M-mode has the advantage of being easy to obtain, as the mitral valve, even when good image quality is difficult, is usually possible to visualize. In the general population, MPI assessed by TDI M-mode provides prognostic value beyond conventional echocardiographic measurements such as LVEF, LVMI and measures of diastolic function, and adds to prediction models including the Framingham Risk Score, the SCORE risk chart or the ESH/ESC risk chart.

Similarly, CMD assessed by TTDE-measured CFVR adds to the prognostic stratification in patients without obstructive CAD and normal left ventricular function, in a subset of patient populations including patients with known ischemic heart disease and in patients with diabetes. As measurement of CFVR requires stress application, we evaluated whether MPI at rest was associated with CFVR. In univariable analysis we found that higher MPI, longer IVCT and shorter ET, but not IVRT, were associated with lower CFVR. In multivariable analysis, higher MPI and higher IVCT remained associated with lower CFVR indicating that CMD impairs systolic, but not diastolic, function. A study of asymptomatic, newly diagnosed diabetic patients without obstructive CAD found a significant correlation between MPI and CFVR. Our study results support these findings and suggest that the association between MPI and CFVR may not be dependent on diabetes. Another study investigated the correlation between TDI parameters and coronary flow assessed by the thrombolysis in myocardial infarction (TIMI) frame count in the absence of obstructive CAD and found a significant correlation between higher MPI and higher TIMI frame counts indicative of reduced microvascular flow. Although data in this area of research are sparse, these studies support our findings of an association between cardiac time intervals and coronary microvascular function.

**Strengths and limitations**

Our study’s strengths included that the population had prevalence (30.6%) of CMD defined by CFVR <2 that was comparable to CMD prevalence reported in other studies. Also, our method validation for all included TDI parameters showed acceptable inter- and intra-reader variability. Limitations include that no asymptomatic controls were examined. We did not calculate...
MPI by conventional PW Doppler tracings of mitral inflow and LV outflow, which could have added to the general applicability of our results. Of note, previously published reference values for MPI in asymptomatic women (n=553) were comparable to MPI mean values observed in our study participants (0.44 vs. 0.45)\textsuperscript{34}. Furthermore, dipyridamole stress examination assesses endothelial independent coronary microvascular function and a potential contribution of endothelial-dependent microvascular function was not examined.

CONCLUSION

In women with AP and no obstructive CAD, CMD defined by CFVR <2.0 is associated with longer IVCT and higher MPI. These results indicate a link between CMD and presence of subtle systolic, but not diastolic LV dysfunction. The prognostic significance of cardiac time intervals in these women warrants further investigation.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Adam Pena MD: Concept/design, data collection, data analysis/interpretation, drafting article, critical revision of article, approval of article, statistics.

Marie Mide Michelsen MD PhD: Data collection, data analysis/interpretation, critical revision of article, approval of article.

Naja Dam Mygind MD PhD: Data collection, data analysis/interpretation, critical revision of article, approval of article.
Ida Gustafsson MD PhD: Concept/design, data interpretation, critical revision of article, approval of article. 
Nis Høst MD PhD: Concept/design, data interpretation, critical revision of article, approval of article. 
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Peter Riis Hansen MD DMSc: Concept/design, data analysis/interpretation, critical revision of article, approval of article, statistics, funding. 
Eva Prescott MD DMSc: Concept/design, data analysis/interpretation, critical revision of article, approval of article, statistics, funding. 

REFERENCES


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### Tables

**Table 1. Clinical characteristics, echocardiographic measures and coronary flow velocity reserve (CFVR).**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Overall (n=389)</th>
<th>CFVR&lt;2 (n=119)</th>
<th>2&lt;CFVR&lt;2.5 (n=132)</th>
<th>CFVR&gt;2.5 (n=138)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean [SD]) years</td>
<td>62.0 (9.7)</td>
<td>64.4 (9.6)</td>
<td>62.4 (9.8)</td>
<td>59.7 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body Mass Index (mean [SD]) kg/m²</td>
<td>27.3 (5.1)</td>
<td>27.4 (5.5)</td>
<td>27.2 (4.7)</td>
<td>27.2 (5.1)</td>
<td>0.794</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>203 (52.2)</td>
<td>75 (63.0)</td>
<td>66 (50.0)</td>
<td>62 (44.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>42 (10.8)</td>
<td>16 (13.5)</td>
<td>15 (11.4)</td>
<td>11 (8.0)</td>
<td>0.158</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>252 (64.8)</td>
<td>74 (62.2)</td>
<td>83 (62.9)</td>
<td>95 (68.8)</td>
<td>0.256</td>
</tr>
<tr>
<td>Non-occlusive atherosclerosis at CAG, n (%)</td>
<td>135 (34.7)</td>
<td>43 (36.1)</td>
<td>52 (39.4)</td>
<td>40 (29.0)</td>
<td>0.208</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>67 (17.2)</td>
<td>24 (20.2)</td>
<td>26 (19.7)</td>
<td>17 (12.3)</td>
<td>0.091</td>
</tr>
<tr>
<td>Heart rate (mean [SD])</td>
<td>69.4 (10.4)</td>
<td>71.7 (11.4)</td>
<td>69.5 (10.0)</td>
<td>67.3 (9.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mean [SD]) mmHg</td>
<td>131.2 (20.9)</td>
<td>130.4 (20.9)</td>
<td>131.3 (18.5)</td>
<td>131.8 (23.2)</td>
<td>0.634</td>
</tr>
<tr>
<td>Diastolic blood pressure (mean [SD]) mmHg</td>
<td>66.8 (10.4)</td>
<td>64.9 (9.4)</td>
<td>66.4 (9.7)</td>
<td>68.8 (11.5)</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Standard echocardiographic measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Overall</th>
<th>CFVR&lt;2</th>
<th>2&lt;CFVR&lt;2.5</th>
<th>CFVR&gt;2.5</th>
<th>β</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (mean [SD]) %</td>
<td>60.3 (5.5)</td>
<td>60.1 (5.8)</td>
<td>61.1 (5.1)</td>
<td>59.7 (5.5)</td>
<td>0.06</td>
<td>(-0.06; 0.17)</td>
<td>0.338</td>
</tr>
<tr>
<td>LVIDd (mean [SD]) cm</td>
<td>4.7 (0.5)</td>
<td>4.6 (0.47)</td>
<td>4.7 (0.50)</td>
<td>4.7 (0.54)</td>
<td>0.222</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMI (mean [SD]) g/m²</td>
<td>69.2 (13.3)</td>
<td>68.7 (12.7)</td>
<td>69.5 (14.2)</td>
<td>69.2 (13.2)</td>
<td>0.750</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAVI (mean [SD]) ml/m²</td>
<td>29.5 (7.7)</td>
<td>29.5 (7.3)</td>
<td>29.1 (8.3)</td>
<td>29.8 (7.5)</td>
<td>0.748</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PW e' (mean [SD]) cm/sec</td>
<td>9.2 (2.2)</td>
<td>9.0 (2.3)</td>
<td>9.2 (2.3)</td>
<td>9.4 (2.1)</td>
<td>0.126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A-ratio (mean [SD])</td>
<td>0.98 (0.27)</td>
<td>0.96 (0.3)</td>
<td>0.99 (0.3)</td>
<td>0.99 (0.2)</td>
<td>0.422</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/e'-ratio (mean [SD])</td>
<td>8.1 (2.4)</td>
<td>8.6 (3.0)</td>
<td>8.1 (2.2)</td>
<td>7.6 (1.8)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceleration time (mean [SD]) ms</td>
<td>182.3 (31.7)</td>
<td>185.5 (31.5)</td>
<td>180.7 (32.1)</td>
<td>181.1 (31.5)</td>
<td>0.295</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Overall</th>
<th>CFVR&lt;2</th>
<th>2&lt;CFVR&lt;2.5</th>
<th>CFVR&gt;2.5</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAAS-inhibitors, n (%)</td>
<td>73 (19.0)</td>
<td>28 (23.7)</td>
<td>23 (17.6)</td>
<td>22 (16.3)</td>
<td>0.140</td>
</tr>
<tr>
<td>Betablockers, n (%)</td>
<td>111 (28.8)</td>
<td>33 (28.0)</td>
<td>43 (32.6)</td>
<td>35 (25.9)</td>
<td>0.687</td>
</tr>
<tr>
<td>Calcium antagonists, n (%)</td>
<td>81 (21.0)</td>
<td>29 (24.4)</td>
<td>29 (22.1)</td>
<td>23 (16.9)</td>
<td>0.142</td>
</tr>
<tr>
<td>Long acting nitrsglycmine, n (%)</td>
<td>27 (6.9)</td>
<td>12 (10.1)</td>
<td>9 (6.8)</td>
<td>6 (4.4)</td>
<td>0.076</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>187 (48.5)</td>
<td>64 (53.8)</td>
<td>62 (47.3)</td>
<td>61 (44.9)</td>
<td>0.159</td>
</tr>
<tr>
<td>Acetylsalicylic acid, n (%)</td>
<td>179 (46.4)</td>
<td>57 (47.9)</td>
<td>71 (53.8)</td>
<td>51 (37.8)</td>
<td>0.092</td>
</tr>
</tbody>
</table>

p-value from trend test: linear regression for continuous variables and logistic regression for discrete variables. CFVR: coronary flow velocity reserve; SD: standard deviation; CAG: coronary angiography; LVEF: left ventricular ejection fraction; LVIDd: left ventricular internal diameter in diastole; LVMI: left ventricular mass index; LAVI: left atrium volume indexed; PW e': peak early diastolic velocity from pulse wave Doppler; RAAS: renin-angiotensin-aldosterone-system.

Table 2. Mitral annular velocities and cardiac time intervals according to coronary flow velocity (CFVR) group

<table>
<thead>
<tr>
<th>Measure</th>
<th>Overall</th>
<th>CFVR&lt;2</th>
<th>2&lt;CFVR&lt;2.5</th>
<th>CFVR&gt;2.5</th>
<th>β</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>s', cm/s</td>
<td>5.9 (0.9)</td>
<td>5.8 (1.0)</td>
<td>5.9 (0.9)</td>
<td>5.9 (0.8)</td>
<td>0.06</td>
<td>(-0.06; 0.17)</td>
<td>0.338</td>
</tr>
<tr>
<td>e', cm/s</td>
<td>-7.0 (1.8)</td>
<td>-6.8 (1.9)</td>
<td>-7.0 (1.8)</td>
<td>-7.1 (1.6)</td>
<td>-0.18</td>
<td>(-0.40; 0.04)</td>
<td>0.113</td>
</tr>
<tr>
<td>a, cm/s</td>
<td>-7.2 (1.4)</td>
<td>-7.3 (1.6)</td>
<td>-7.1 (1.5)</td>
<td>-7.2 (1.2)</td>
<td>0.06</td>
<td>(-0.12; 0.24)</td>
<td>0.485</td>
</tr>
<tr>
<td>IVCT, ms</td>
<td>32.8 (11.4)</td>
<td>37.7 (13.0)</td>
<td>30.8 (10.6)</td>
<td>30.6 (9.3)</td>
<td>-3.45</td>
<td>(-4.82; -2.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>99.2 (16.4)</td>
<td>99.5 (17.3)</td>
<td>99.6 (16.7)</td>
<td>98.5 (15.3)</td>
<td>-0.48</td>
<td>(-2.49; 1.54)</td>
<td>0.643</td>
</tr>
<tr>
<td>ET, ms</td>
<td>298.1 (26.3)</td>
<td>293.7 (28.7)</td>
<td>296.3 (25.4)</td>
<td>303.5 (24.2)</td>
<td>4.97</td>
<td>(1.77; 8.16)</td>
<td>0.002</td>
</tr>
<tr>
<td>MPI</td>
<td>0.45 (0.08)</td>
<td>0.47 (0.10)</td>
<td>0.44 (0.07)</td>
<td>0.43 (0.08)</td>
<td>-0.02</td>
<td>(-0.03; -0.01)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
All parameters are listed as means (standard deviations[SDs]). \( \beta \), 95% CI, and p-values from trend-test (regression analysis). \( s' \): peak systolic velocity; \( e' \): peak early diastolic velocity; \( a' \): peak late diastolic velocity; IVCT: isovolumic contraction time; IVRT: isovolumic relaxation time; ET: ejection time; MPI: myocardial performance index

**FIGURE LEGENDS**

Figure 1
Left: apical 4-chamber TDI view with M-mode line positioned (top) and apical 4-chamber grayscale (bottom); Right: tissue Doppler curved-anatomical M-mode color diagram. MVC: mitral valve closing; AVO: aortic valve opening; AVC: aortic valve closing; MVO: mitral valve opening

Figure 2
Scatterplot of coronary flow velocity reserve (CFVR) vs isovolumic contraction time (IVCT). R-squared and p-value from multivariable regression analysis

Figure 3
Scatterplot plot of coronary flow velocity reserve (CFVR) vs myocardial performance index (MPI). R-squared and p-value from multivariable regression analysis

Figure 4
Bland-Altman plots of intra-reader variability (n=20), inter-reader variability (n=20) and intra-reader variability of repeat examinations (n=10) of MPI showing mean difference (*solid lines*) and 95% limits of agreement (*dotted lines*)
Intra−reader variability

Inter−reader variability

Repeat MPI variability

Difference between MPI measurements

echo_14356_f4.eps