Coronary Microvascular Dysfunction and Myocardial Contractile Reserve in Women With Angina and No Obstructive Coronary Artery Disease

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Abstract

Background

Coronary microvascular dysfunction (CMD) is a potential cause of myocardial ischemia and may affect myocardial function at rest and during stress. We investigated whether CMD was associated with left ventricular diastolic and systolic function at rest and during pharmacologically induced hyperemic stress.

Method

We included 963 women with angina, left ventricular ejection fraction (LVEF) >45%, and an invasive coronary angiogram without significant stenosis (<50%). LVEF, parameters of diastolic function, speckle tracking-derived global longitudinal strain (GLS) and coronary flow velocity reserve (CFVR) were assessed by transthoracic echocardiography at rest and during dipyridamole stress. Participants were divided into three groups according to CFVR and CMD was defined as CFVR <2. The GLS and LVEF reserves were defined as the absolute increases in GLS and LVEF during stress.

Results

CFVR was successfully measured in 919 (95%) women and CMD was present in 26%. CMD was associated with older age and a higher resting heart rate. Women with CMD had a reduced GLS reserve (p=0.005), while we found no association between CFVR and LVEF at rest, GLS at rest, or the LVEF reserve, respectively. GLS reserve remained associated with CFVR (p=0.002) in a multivariable regression analysis adjusted for age, hemodynamic variables and GLS at rest. In age-adjusted analysis, women with low CFVR had no signs of diastolic dysfunction measured by echocardiography at rest.

Conclusion
The GLS reserve was significantly lower in women with CMD. The mechanisms underlying the association between CMD and GLS reserve warrant further study.
**Introduction**

The combined presentation of angina pectoris and no obstructive coronary artery disease (CAD) increases risk of major adverse cardiovascular events [1]. Coronary microvascular dysfunction (CMD) is increasingly recognized as a potential cause of angina in these patients [2]. However, knowledge of the linkage between CMD and myocardial structural and functional alterations remains limited [3].

CMD includes an abnormal regulation of the coronary circulation in response to increasing oxygen demand that may contribute to myocardial ischemia [4]. The coronary microcirculation regulates myocardial perfusion via endothelial-dependent and -independent pathways, with the latter being determined by, for example, intraluminal coronary pressure and myocardial metabolic activity [5]. The endothelial independent function of the coronary microcirculation can be determined by assessment of the coronary flow velocity reserve (CFVR) in response to adenosine or dipyridamole [5, 6]. Impaired CFVR is associated with cardiovascular risk factors [7–9] and is a robust predictor of adverse prognosis in various patient populations [7,10–14].

It has been suggested that CMD can cause left ventricular (LV) diastolic dysfunction and contribute to development of heart failure with preserved ejection fraction but limited data exist in support of this hypothesis [15–17]. Further, it is unknown whether CMD affects the LV systolic function. Speckle tracking derived global longitudinal strain (GLS) determined by transthoracic echocardiography can detect early LV dysfunction at rest and provides incremental information compared with traditional measures such as LV ejection fraction (LVEF). GLS is a marker of future cardiovascular adverse events in both community-based cohorts and in patients with existing cardiovascular disease [18–21]. GLS reserve measured by dipyridamole-induced stress is a relatively novel measure that gives insight into the LV contractile reserve with potential prognostic value [22] and measurement of GLS reserve has been introduced in guidelines for the clinical use of stress echocardiography [23].
We investigated whether CMD was associated with LV systolic and diastolic function assessed by echocardiographic parameters at rest and during dipyridamole-induced stress in women with angina and no significant CAD.

Methods

Population

The study population consisted of participants from the prospective iPOWER (improving diagnosis and treatment of women with angina pectoris and microvascular disease) cohort. This cohort comprised women (18-80 years) referred for a clinically indicated diagnostic coronary arteriography (CAG) due to chest pain suggestive of angina pectoris where no obstructive CAD (<50% stenosis) was found. Detailed description of recruitment, in- and exclusion criteria of the patient population and the acquirement of baseline descriptive measures has been given previously [24–26].

Echocardiography

Participants underwent a standard resting transthoracic echocardiography 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). A small team of investigators performed the image acquisition and analysis assuring good inter-analyzer reproducibility [24]. Participants were instructed to be abstinent from caffeine and food containing significant amount of methylxanthine (coffee, tea, chocolate, coca cola and banana) for 24 hours. Medication containing dipyridamole was paused for 48 hours, anti-ischemic agents (long-lasting nitroglycerin, beta-blockers, calcium antagonist, ivabradine etc.), anti-hypertensive medication and diuretics for 24 hours and short-lasting nitroglycerin for 1 hour before the examination. Abstinence from these substances was confirmed verbally before initiation of the examinations.
Examination at rest

The 2-dimensional images of the LV in apical long axis, 2- and 4-chamber views were acquired at frame rates between 60-90 frames/s adjusted as close to the participants’ heart rate as possible. GLS was measured using software for speckle tracking analysis (Q-analysis, GE EchoPAC v.112, Norway). The LV endocardial border was traced in all three views, and the automatically created region of interest was manually adjusted to the thickness of the myocardium avoiding pericardial borders until tracking was considered optimal. Segments were discarded if tracking was persistently poor after readjustment of the region of interest. Subsequently, deformation parameters were automatically obtained for all accepted LV segments. Aortic valve closure was defined in the tissue Doppler imaging view as a characteristic shift from positive to negative velocity of the basal septal wall movement. For this study GLS was calculated as the average of all accepted segmental values of end systolic strain (Peak S) [27]. Moreover strain rate segmental values were averaged. We have previously reported good inter-analyzer reproducibility for GLS [24]. In a sub-analysis testing robustness of results only 3 discarded segments were permitted according to recommendations in guidelines [27]. Furthermore, we performed separate analysis using peak longitudinal strain (Peak G) and strain calculated by the EchoPAC program algorithm (GE EchoPAC v.112, Norway).

LVEF was acquired as a semi-automated biplane calculation (Auto-EF tool, GE EchoPAC v.112, Norway). Further, stroke volume was calculated by measuring the diameter of the LV outflow tract (LVOT) in a 2D parasternal long-axis image and tracing the corresponding velocity time integral of a 5 chamber LVOT pulsed wave image using the algorithm \( \pi (LVOT \text{ diameter}/2)^2 \times \text{LVOT velocity time integral} \). Cardiac output was calculated as stroke volume multiplied by heart rate.

Measurements of LV internal dimensions, LV mass index (LVMI), LV hypertrophy and left atrium volume index (LAI) by the Volume Method of Discs were performed and calculated according to European and American recommendations [28–30].
Echocardiographic parameters of diastolic function including the ratio between early (E) and late (A) peak velocities of the mitral inflow, E/A, and pulsed wave tissue Doppler velocities of the mitral annulus in early diastole in the lateral wall (e’) were used as surrogates of diastolic relaxation and LV compliance, the deceleration time (DT) as a surrogate of early LV stiffness, and E/e’ as surrogate estimate of LV filling pressure, respectively.

Moreover, LV filling pressure was categorized as normal or high by a modified algorithm from the recommendations from the American and European Society of Echocardiography in individuals with preserved LVEF, i.e. normal filling pressures if E/e’ <8, or E/e’ 8-12 and LAI <34 mL/m2, respectively, and high filling pressures if E/e’ was 8-12 and LAI >34, or E/e’ >12, respectively [30].

Dipyridamole stress examination

Participants underwent a transthoracic Doppler echocardiography (TTDE) of the left anterior descending artery (LAD) during rest and high-dose intravenous dipyridamole stress (0.84 mg/kg) over 6 minutes to obtain coronary flow velocities (CFV) at baseline and at maximal hyperemia using a 2.7-8 MHz transducer (GE Vivid 6S probe) as previously described [25,26]. CFVR was calculated as the ratio between peak diastolic CFV during stress and during rest. Two independent experts double read measurements. We have previously reported a more detailed description of the CFVR measurement [25,26]. All CFVR measurements were assigned a technical quality score from 0-3, and thus categorized as either non-feasible (score 0), low quality (score 1), medium quality (score 2) and high quality (score 3), respectively, based on a semi-quantitative assessment [26]. Two-dimensional images of the LV in apical long axis, 2- and 4-chamber views were acquired at hyperemia with frame rates adjusted as close to the patient’s heart rate as possible (60-90 frames/s). Strain and LVEF measurements were performed as described above. LV contractile reserve parameters included absolute increases of GLS (ΔGLS), LVEF (ΔLVEF), and strain rate (Δstrain rate) from rest to peak hyperemia. Blood pressure was obtained at rest and at maximal heart rate
during peak dipyridamole stress. Heart rates were extracted from the continuously ECG registered during the echocardiographic examination.

**Statistical analyses**

Continuous variables with a Gaussian distribution are described as mean (standard deviation, SD), and continuous variables with a non-Gaussian distribution as median (interquartile range, IQR). Counts in % were used for categorical variables. Normal distribution was assessed graphically.

GLS and strain rate were treated as numerical absolute values in our data analyses. To investigate associations between CMD and baseline descriptive measures, hemodynamic variables, and echocardiographic parameters, women with angina were divided into three CFVR groups according to current guidelines for determination of CMD using cut-off values of 2.0 and 2.5 [31,32]. Age-adjusted trend tests obtained by multivariable linear and logistic regression analysis were used to evaluate the distribution of baseline descriptive measures, hemodynamic variables, and LV diastolic and systolic parameters between the three CFVR groups.

To assess the robustness of our results, subanalyses excluding participants with atrial fibrillation, participants with a poor quality CFVR examination, and speckle tracking analyses where more than 3 out of the 18 segments were discarded, respectively, were undertaken.

To explore predictors of ΔGLS, multivariable linear regression analysis was performed. All potential explanatory variables with a priori-defined hypothesis including age, CFVR, baseline GLS, hemodynamic variables at rest and at hyperemia, and cardiovascular risk factors (Table 3) were tested as determinants of ΔGLS and discarded with a cut-off level of p ≥0.10. Assumptions of linearity, variance homogeneity and Gaussian distribution of residuals were assessed graphically.

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 participants gave written informed consent after receiving oral and written information about the study.

**Results**

**Study population**

Out of the 963 participants included, 919 (95%) had a successfully measured CFVR. Participants with low CFVR were significantly older and had a higher resting heart rate. Participants with low CFVR had an attenuated increase in systolic and diastolic blood pressure during hyperemia induced by dipyridamole (Table 1). Median (IQR) CFVR was 2.33 (1.98-2.76). A total of 241 (26%) participants had a CFVR ≤2, 318 (35%) had a CFVR between 2 and 2.5, and 360 (39%) had a CFVR >2.5.

**Association between CMD and LV diastolic and systolic function**

Due to poor image quality echocardiographic strain examination was not feasible in 43 (5%) subjects at rest. In age-adjusted analysis, baseline GLS did not differ between CFVR groups.

Due to symptoms during dipyridamole infusion 103 (11%) participants did not wish to prolong the examination for the additional recording of images for strain analysis. Further 48 (5%) strain examinations were not feasible at peak hyperemia. GLS increased markedly between rest and pharmacologically induced hyperemia (p<0.001). Women with CMD had a significantly lower GLS at hyperemia and a lower ΔGLS. A low strain rate at hyperemia and a low Δstrain rate were also
associated with CFVR groups (Table 2). The higher resting heart rate in women with CMD did not explain the relation between ΔGLS and CFVR groups (see ‘Predictors of ΔGLS’, below). After age-adjustment, no parameters of diastolic function differed significantly between CFVR groups (Table 2).

Excluding participants with atrial fibrillation (n=21) or participants with a poor quality CFVR examination (n=80) yielded similar results. In speckle tracking analysis, more than 3 out of the 18 segments were discarded due to poor tracking in 47% at baseline examination and 51% at hyperemia leaving 36% of examinations with a baseline and stress speckle tracking analyses with less than 3 segments discarded for a sub-analysis for stress-induced change in GLS. Excluding these examinations also yielded similar results. Further, results were similar when studying the GLS based on peak systolic strain and GLS calculated from the automatized EchoPAC program algorithm.

**Predictors of GLS reserve**

The association between ΔGLS and CFVR is shown in Figure 1. To further explore whether GLS at rest, hemodynamic or cardiovascular factors explained the association between CFVR and ΔGLS, we performed a multivariable adjusted regression analysis. Reduced ΔGLS was associated with a lower CFVR, a higher GLS, heart rate and systolic blood pressure at rest and a higher proportion of patients with hypercholesterolemia (Table 3). The regression model explained 21% of the variation in the GLS reserve ($r^2=0.21$).

Including only examinations where less than 3 out of the 18 segments were discarded from analysis resulted in similar results, just as results were similar for GLS based on peak systolic strain and GLS calculated from the EchoPAC program algorithm.

**Discussion**
In this study of women with angina and no obstructive CAD, we found that CMD determined by CFVR <2.0 was associated with a reduced contractile response to hyperemic stress as determined by ΔGLS. CMD was not associated with LV systolic or diastolic echocardiographic parameters at rest.

**Association between baseline GLS and CFVR**

Studies in patients with CAD have found a significant association between reduced CFVR and GLS at rest [33–36]. In the present study of patients with no obstructive CAD we found no such association. In patients with CAD, reduced CFVR usually represents a combined result of flow-limiting epicardial coronary stenosis, CMD, and myocardial tissue loss and remodeling, whereas CFVR impairment in our patients would be more exclusively due to CMD. It is conceivable that our patient population generally represented an earlier stage of disease where alterations of the myocardium leading to contractile dysfunction at rest were not apparent. In potential support of this hypothesis, a study of diabetic patients (n=22) and non-diabetic (n=26) controls without CAD also found no association between GLS and CFVR [37].

**Association between CFVR and GLS reserve**

We found that a reduced CFVR was associated with reduced GLS reserve during dipyridamole-induced stress. Prior research in this area is sparse. One study found that the GLS reserve assessed by exercise stress echocardiography was significantly lower in women with angina, no obstructive CAD and a positive stress test (cardiac syndrome X; n=22) compared with healthy controls (n=20) but CFR was not examined in that study [38]. In another study including subjects without high-grade (>70%) epicardial coronary stenosis at CAG (n=45; 67% men) the invasively measured index of microcirculatory resistance was associated with LV contractile reserve measured by strain imaging during dobutamine stress echocardiography, whereas coronary flow reserve measured by a thermodilution technique was not correlated to GLS reserve [39]. However, coronary flow reserve measured by the thermodilution technique is not as solidly established as CFVR assessed by TTDE.
in terms of prognostic predictive value and reproducibility. The current sum of evidence supports the hypothesis that CMD contributes to subtle changes in myocardial contractile function that can be unmasked by pharmacological (or physiological) stress. Our research group has recently published a study showing no association between CFVR and myocardial fibrosis assessed by cardiac magnetic resonance imaging in women with angina but no obstructive CAD participating in the current iPOWER population [40]. This indicates that the reduced LV contractile reserve in patients with CMD is unlikely to be explained by increased myocardial stiffness (as also supported by the lack of association found between CFVR and LV diastolic dysfunction) and other factors probably play a predominant role, e.g. a supply/demand mismatch of myocardial perfusion caused by CMD.

**Association between LV diastolic function and CFVR**

CMD, which is present in up to 50% of patients with angina and no obstructive CAD, has also been found in many patients with heart failure with preserved ejection fraction [41,42]. Therefore CMD has been suggested to be linked to diastolic dysfunction and, ultimately, heart failure [15–17,42]. This association could be a manifestation of causality or, for example, existence of shared causal factors. In support of causality, CMD can result in repetitive ischemia of the myocardium, which could cause fibrosis and unfavorable LV remodeling [42]. However, CMD and diastolic dysfunction could also be linked by shared underlying factors such as LV hypertrophy and fibrosis caused e.g. by hypertension and other cardiovascular risk factors [43–45]. However, in the present study of patients with no obstructive CAD we found no such association. In patients with CAD (n=40) and patients with heart failure with reduced ejection fraction (n=47), CMD has been shown to correlate with indices of LV diastolic dysfunction [46,47]. In patients (n=72) with inflammatory bowel disease, lateral e’/a’ ratio was predictive of CFVR [48] and in patients (n=67) with diabetes the E/e’ was associated with CFVR [49]. Further, a study (??% men) including patients with angina, no coronary artery stenosis and preserved LVEF showed that those with diastolic heart failure (n=155) had a more impaired coronary microcirculation determined by angiographic indices than those without
heart failure (n=131), although the authors did not adjust for differences in cardiovascular risk factors between groups [16]. The association between CMD and LV diastolic function in diverse patient populations thus clearly require more study.

**Strengths and limitations**

The present study included a large cohort of women with angina and no obstructive CAD that were consecutively recruited. The baseline CFV measured by TTDE is influenced by the angle between the ultrasound beam and the direction of blood flow in the interrogated LAD segment, which is a limitation for this parameter. However, as CFVR is the ratio between hyperemic and baseline CFV and not an absolute value, angle dependency of CFVR measurement is likely to be diminished [50]. Non-invasive CFVR examination with dipyridamole as the pharmacological stressor examines endothelial independent coronary microvascular function and we did not assess endothelial-dependent responses due to ethical and logistic concerns. One study found an association between coronary vasospastic response to acetylcholine infusion at invasive CAG and impaired LV diastolic function during the infusion in women with angina and no obstructive CAD [51]. It is thus possible that endothelial-dependent microvascular abnormalities may have contributed to our results.

**Conclusion**

In women with angina and no obstructive CAD, the GLS reserve was significantly lower in subjects with CMD. The mechanisms underlying the association between CMD and GLS reserve warrant further study.

**Acknowledgements**

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The University of Copenhagen

**Conflict of interest**

The authors have nothing to disclose.
REFERENCES


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## Tables

Table 1. Baseline characteristics according to coronary flow velocity reserve (CFVR) level

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CFVR &lt; 2 n=241</th>
<th>2&lt;CFVR&gt;2.5 n=318</th>
<th>CFVR&gt;2.5 n=360</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>65.0 (9.2)</td>
<td>62.0 (9.7)</td>
<td>60.0 (9.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>143 (59)</td>
<td>168 (53)</td>
<td>156 (44)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>161 (67)</td>
<td>205 (65)</td>
<td>214 (60)</td>
<td>0.51</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>40 (17)</td>
<td>42 (13)</td>
<td>35 (10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>117 (49)</td>
<td>170 (55)</td>
<td>190 (54)</td>
<td>0.64</td>
</tr>
<tr>
<td>Smoking (current), n (%)</td>
<td>46 (19)</td>
<td>57 (18)</td>
<td>46 (13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²), mean (SD)</td>
<td>27.4 (5.8)</td>
<td>27.3 (5.4)</td>
<td>26.9 (5.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Heart rate at rest (beat/min), mean (SD)</td>
<td>70.6 (11.7)</td>
<td>69.5 (10.7)</td>
<td>67.2 (9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP at rest (mmHg), mean (SD)</td>
<td>134 (22)</td>
<td>133 (21)</td>
<td>133 (22)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diastolic BP at rest (mmHg), mean (SD)</td>
<td>75 (23)</td>
<td>73 (20)</td>
<td>73 (14)</td>
<td>0.41</td>
</tr>
<tr>
<td>Heart rate at peak hyperemia (beat/min), mean (SD)</td>
<td>93.0 (13.8)</td>
<td>96.5 (12.8)</td>
<td>97.3 (13.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Systolic BP at peak hyperemia (mmHg), mean (SD)</td>
<td>131 (23)</td>
<td>132 (22)</td>
<td>136 (24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP at peak hyperemia (mmHg), mean (SD)</td>
<td>69 (14)</td>
<td>70 (13)</td>
<td>74 (14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Parameters are listed as mean (standard deviation). *p-value from age-adjusted trend test by multivariable linear regression. p<0.05 is marked with bold type. BP: Blood pressure.
Table 2. Echocardiographic parameters at rest and peak stress according to coronary flow velocity reserve (CFVR) level

<table>
<thead>
<tr>
<th>Systolic parameters</th>
<th>CFVR &lt; 2 n=241</th>
<th>2&lt;CFVR&gt;2.5 n=318</th>
<th>CFVR&gt;2.5 n=360</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS at rest (%) mean (SD)</td>
<td>21.2 (2.8)</td>
<td>21.5 (2.6)</td>
<td>21.3 (2.6)</td>
<td>0.31</td>
</tr>
<tr>
<td>GLS at hyperemia (%) mean (SD)</td>
<td>23.1 (3.0)</td>
<td>23.3 (2.6)</td>
<td>23.6 (2.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>ΔGLS (%) mean (SD)</td>
<td>1.8 (2.3)</td>
<td>1.8 (2.4)</td>
<td>2.4 (2.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Strain rate at rest (s⁻¹) mean (SD)</td>
<td>1.28 (0.20)</td>
<td>1.30 (0.20)</td>
<td>1.26 (0.18)</td>
<td>0.33</td>
</tr>
<tr>
<td>Strain rate at hyperemia (s⁻¹) mean (SD)</td>
<td>1.55 (0.25)</td>
<td>1.59 (0.23)</td>
<td>1.61 (0.23)</td>
<td>0.02</td>
</tr>
<tr>
<td>Δstrain rate (s⁻¹) mean (SD)</td>
<td>0.29 (0.22)</td>
<td>0.30 (0.21)</td>
<td>0.36 (0.22)</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEF at rest (%) mean (SD)</td>
<td>58.6 (6.2)</td>
<td>59.4 (5.9)</td>
<td>58.1 (5.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>LVEF at hyperemia (%) mean (SD)</td>
<td>62.3 (6.7)</td>
<td>62.6 (7.2)</td>
<td>62.0 (6.1)</td>
<td>0.41</td>
</tr>
<tr>
<td>ΔLVEF (%) mean (SD)</td>
<td>3.7 (6.1)</td>
<td>3.1 (7.2)</td>
<td>3.8 (6.2)</td>
<td>0.88</td>
</tr>
<tr>
<td>s’, mean (SD)</td>
<td>8.09 (1.42)</td>
<td>8.22 (1.45)</td>
<td>8.11 (1.29)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stroke volume at rest (mL) mean (SD)</td>
<td>80.0 (19.4)</td>
<td>80.1 (17.6)</td>
<td>78.1 (18.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>Cardiac output at rest (L/min) mean (SD)</td>
<td>5.6 (1.5)</td>
<td>5.5 (1.4)</td>
<td>5.2 (1.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Left ventricular and atrial dimensions

| Left atrial mass index, mean (SD)               | 72.1 (14.2)    | 71.2 (14.0)      | 72.3 (13.6)    | 0.34|
| Left atrium volume index, mean (SD)            | 30.4 (8.4)     | 29.6 (7.8)       | 28.8 (7.6)     | 0.13|

Left ventricular diastolic function

| e’, mean (SD)                                   | 9.58 (2.59)    | 10.05 (2.90)     | 10.21 (2.76)   | 0.53|
| E/e’ ratio, mean (SD)                          | 8.40 (3.31)    | 7.75 (2.50)      | 7.49 (2.38)    | 0.06|
| E/A ratio, mean (SD)                           | 1.00 (0.29)    | 1.04 (0.30)      | 1.05 (0.29)    | 0.79|
| Deceleration time, mean (SD)                   | 187.7 (32.7)   | 181.1 (31.36)    | 180.8 (30.7)   | 0.14|
| High filling pressure†, n (%)                  | 49 (22)        | 44 (15)          | 46 (13)        | 0.35|

*p-value from age-adjusted trend test by multivariable linear or logistic regression. ** p<0.05 is marked with bold type. GLS: global longitudinal end systolic strain. LVEF: left ventricular ejection fraction. †Filling pressure was estimated as normal if E/e’<8 or E/e’ 8-12 and LAI <34 mL/m², respectively, and high if E/e’ 8-12 and LAI >34 or E/e’ >12, respectively.
Table 3. Predictors of global longitudinal end systolic strain reserve (ΔGLS): Results from multivariable linear regression in women with angina and no coronary artery disease.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>p-value*</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.0097</td>
<td>-0.028; 0.0082</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>CFVR</td>
<td>0.378</td>
<td>0.135; 0.621</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>GLS at rest</td>
<td>-0.400</td>
<td>-0.460; -0.339</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Heart rate at rest</td>
<td>-0.024</td>
<td>-0.040; -0.009</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Heart rate at peak hyperemia</td>
<td>-0.005</td>
<td>-0.020; 0.011</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Systolic BP at rest</td>
<td>-0.008</td>
<td>-0.016; -0.0009</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP at rest</td>
<td>0.006</td>
<td>-0.020; 0.032</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Systolic BP at peak hyperemia</td>
<td>-0.002</td>
<td>-0.016; 0.011</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP at peak hyperemia</td>
<td>-0.007</td>
<td>-0.032; 0.017</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index, mean (SD)</td>
<td>0.38</td>
<td>-0.048; 0.013</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>-0.25</td>
<td>-0.57; 0.081</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>-0.33</td>
<td>-0.82; 0.15</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Smoking (current), n (%)</td>
<td>-0.24</td>
<td>-0.67; 0.18</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>-0.41</td>
<td>-0.73; -0.09</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>-0.04</td>
<td>-0.36; 0.27</td>
<td>0.70</td>
<td></td>
</tr>
</tbody>
</table>

*p-value obtained by multivariable linear regression analyses with ΔGLS as outcome variable. **p-value obtained in final model by multivariable linear regression analyses with ΔGLS as outcome variable (n=671 in final model). p<0.05 is marked with bold type. CI: confidence interval. GLS: Global longitudinal end systolic strain. CFVR: Coronary flow velocity reserve. BP: Blood pressure.