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Post-systolic shortening predicts heart failure following acute coronary syndrome☆

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ABSTRACT

Background: Post-systolic shortening (PSS) is a novel echocardiographic marker of myocardial dysfunction. Our objective was to assess the prognostic value of PSS in patients following acute coronary syndrome (ACS) who underwent percutaneous coronary intervention (PCI).
Methods: A total of 428 patients hospitalized for ACS (mean age 64 ± 12 years, male 73%) underwent speckle tracking echocardiography following treatment with PCI (median 2 days). The individual endpoints were heart failure (HF), myocardial infarction (MI) and all-cause death. We excluded known HF. Presence of PSS was defined as post-systolic displacement ≥20% of maximum strain in one cardiac cycle. The post-systolic index (PSI) was defined as (100 × [maximum-strain cardiac cycle − peak-systolic strain])/(maximum-strain cardiac cycle)].
Results: During median follow-up of 3.7 years (IQR 0.3, 5.2), 155 patients (36%) experienced HF, 52 (12%) had MI and 87 (20%) died from all causes. Patients experiencing HF had more walls displaying PSS (3.2 vs. 1.9 walls) and higher PSI (22% vs. 12%) ($P < 0.001$ both). In Cox proportional hazards models adjusted for baseline characteristics, invasive and echocardiographic measurements, the risk of HF increased incrementally with increasing number of walls with PSS (HR 1.28 95%CI 1.12–1.46, $P < 0.001$ per 1 increase in walls with PSS). The PSI remained an independent predictor of HF after adjustment (HR 1.61 95%CI 1.21–2.12, $P = 0.001$ per 1% increase). In the same adjusted models, MI and all-cause death were not significantly associated with PSS.
Conclusion: Presence of PSS provides novel and independent prognostic information regarding the risk of future HF in patients with ACS following PCI.

1. Introduction

A frequent complication following acute coronary syndrome (ACS) is occurrence of adverse cardiovascular events, including heart failure (HF) [1]. Identification of patients with increased risk of cardiovascular outcome is crucial to reduce morbidity and mortality following ischemic events [2]. With regard to HF, the first signs and symptoms of may be non-specific, explaining why early appraisal and close monitoring is of urgent importance. However, in the clinical setting non-invasive and reliable prognostic markers of future cardiovascular events remain limited.

Speckle tracking echocardiography (STE) has enhanced the ability to detect and quantify subtle changes in cardiac deformational patterns, including the occurrence of post-systolic shortening (PSS) (Fig. 1A–B). Several clinical studies have indicated the superiority of PSS over conventional echocardiographic measurements in detecting acute ischemia [3–5]. More recent studies have shown how assessment of PSS after myocardial ischemia and reperfusion was associated with recovery of left ventricular (LV) systolic function [6,7]. Our group has previously investigated the prognostic utility of PSS; specifically, PSS identified patients with a two-fold increased risk of HF following ST-segment elevated myocardial infarction (STEMI) [8]. Hence, PSS may represent a novel and clinically valuable measure to determine the magnitude of functional recovery following ischemic events.

In this study we investigated a representative group of ischemic diagnoses, namely patients suffering from ACS, and sought to examine whether assessment of PSS after revascularization provides independent and novel prognostic information on the risk of long-term adverse cardiovascular events.

2. Methods

2.1. Population

This was a retrospective observational cohort study. From January 2003 to November 2008 a total of 5003 patients underwent percutaneous coronary intervention (PCI) at the Department of Cardiology, Herlev and Gentofte Hospital, Copenhagen University,

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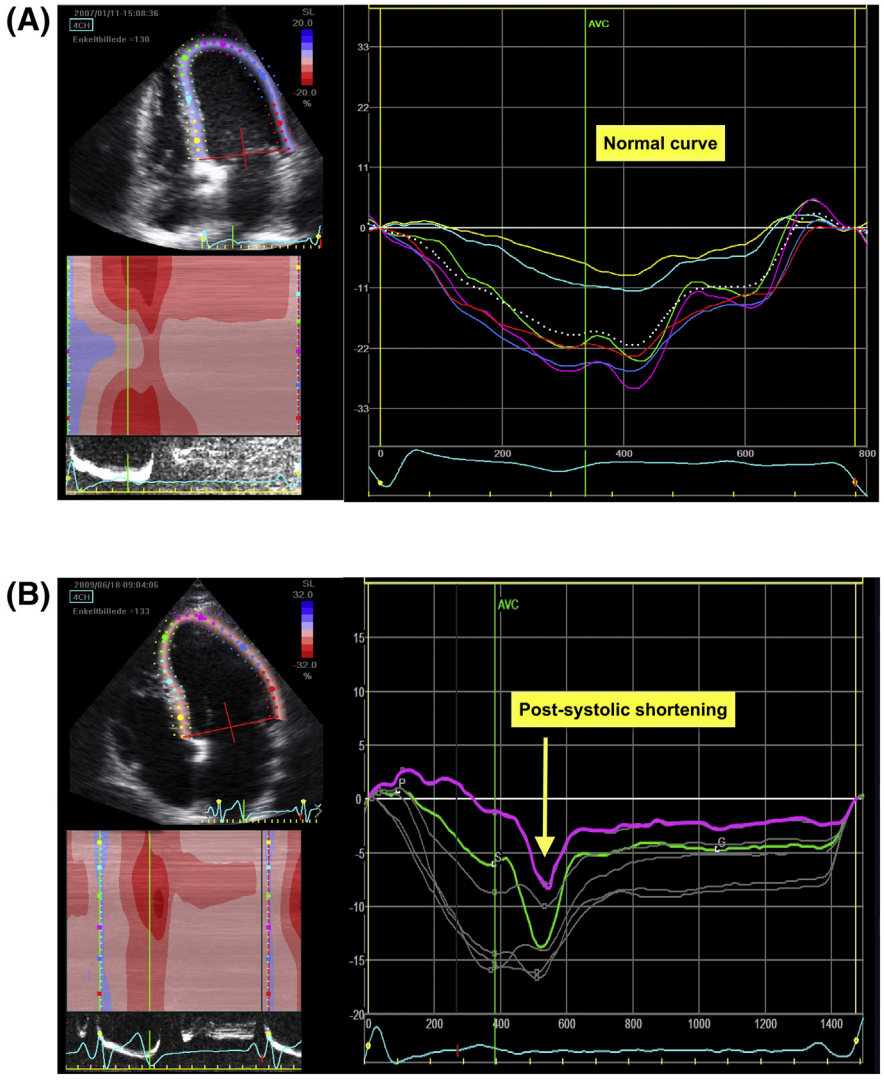

Fig. 1. A–B: Screen captures of two-dimensional speckle tracking echocardiography with longitudinal strain profiles of the left ventricle. (A) Normal strain profile with little or no sign of post-systolic shortening. (B) Strain profile where the green and purple segments exhibit post-systolic shortening.

Denmark, which serves as hub for invasive coronary interventions for 10 non-invasive cardiology departments. A substantial number of patients were transported back to their local hospital following PCI, however, we identified a total of 580 patients suffering from ACS who remained at Herlev and Gentofte Hospital post PCI. We defined ACS as one of the following: ST-segment elevated myocardial infarction (STEMI), non-STEMI (NSTEMI) and unstable angina. All of the 580 patients had an echocardiogram performed a median of 2 days after the PCI (interquartile range (IQR) 1–3 days). Exclusion criteria were: non-sinus rhythm, inter-ventricular conduction disturbances, missing images, inadequate image quality, uncertainty about time of echocardiogram and prevalent HF. A total of 428 were included in the present cohort. The study was approved by the Danish Data Protection Agency and complied with the principles outlined in the 2nd Declaration of Helsinki. The first and senior author have full access to the data and take responsibility for its integrity (PB, TBS). All authors have read and approved the manuscript as written.

2.2. Outcomes

Information regarding cardiovascular outcomes, comprising incident HF, acute myocardial infarction (AMI), and all-cause death, were collected from the Danish National Board of Health's Patient Registry and the Danish Register of Causes of Death using the International Classification of Disease, 10th edition (ICD-10). We defined incident HF as ICD-10 code I50 and AMI as I21. The ICD-10 codes for the respective endpoints were assigned by physicians at the time of diagnosis. The accuracy of a diagnosis of HF in Danish registries has previously been validated [9]. Outcome data were available for all enrolled patients. Additionally, in a series of sensitivity analyses we examined a composite endpoint consisting of: incident HF, AMI and all-cause death.

2.3. Echocardiography

Echocardiographic examinations were carried out using GE Vivid (GE Healthcare, Little Chalfont, United Kingdom) by experienced clinicians and sonographers. Images were stored offline in a GE Healthcare vault and subsequently analyzed with echocardiographic software (EchoPac version 113, GE Healthcare, Horten, Norway) by an experienced physician blinded to all clinical and outcome data.

2.4. Conventional echocardiography

Conventional echocardiography was performed in resting condition and evaluated by the standard 16 segments model according to current guideline recommendations [10]. Simpson's modified biplane method was used in the apical two and four-chamber view to obtain LV ejection fraction (LVEF) and the left atrial volume. LV mass index (LVMI) was calculated by dividing LV mass by body surface area. In the apical four-chamber view, pulsed wave Doppler was used to determine peak transmitral early (E) and late (A) diastolic inflow velocity and deceleration time (DT). Tissue Doppler was used to measure septal and lateral peak early diastolic longitudinal mitral annular velocity (e′), that were averaged to provide a mean value of e′.

2.5. Speckle tracking echocardiography

Two-dimensional STE was performed in the apical two-, three- and four-chamber views with an average of 77 frames per second (standard deviation (SD): 24 frames/s). Six myocardial walls were examined: the septal, lateral, posterior, inferior, anterior and anteroseptal myocardial wall. Each wall consisted of a basal, mid and apical segment, thus providing a total of 18 segments. In end systole a semi-automated function defined

a region of interest (ROI), allowing tracing of the endocardial border. The responsible investigator visually assessed the ROI to ensure correct tracking of speckles and width, and when necessary this was manually re-defined. Tracings were regarded as adequate when they covered the entire myocardial wall, spanned from the endocardium to the myo-epicardial border and motion of speckles was visible. Number of included segments in the strain analyses are listed in Supplemental Table 1. Global longitudinal strain (GLS) was calculated from peak global strain values (describing maximum strain in cardiac cycle) [11].

2.6. Post-systolic measurements

The post-systolic index (PSI) was derived from one cardiac cycle and defined as: (100 × [maximum strain in cardiac cycle − peak systolic strain])/(maximum strain in cardiac cycle). If the minimum segmental length was within the systole, PSI was set to zero. We calculated PSI as the average value obtained from all myocardial wall segments. In order to qualitatively assess the number of walls with PSS, we calculated values of $PSI_{segmental}$ for each wall segment (basal/mid/apical) within each myocardial wall. If a single wall segment within a myocardial wall exhibited $PSI_{segmental} \geq 20\%$, the wall was categorized as having presence of PSS. Our laboratory has previously reported good inter- and intra-reader agreement with only a small bias for PSS [12].

2.7. Statistical analysis

All analyses were performed using Stata SE version 14.2 (StataCorp LP, College Station, TX).

Baseline characteristics for the population were stratified according to number of walls displaying PSS and quartiles of PSI. We calculated P for trend using linear regression models and Chi squared test for trend. All variables used in the present manuscript were tested for Gaussian distribution using qqplot and when necessary converted using a natural logarithmic transformation. The latter applied to PSI. Descriptive data for PSI was presented on the original scale as mean ± SD, and in statistical analysis we used the logarithmic transformed data. Event rates are presented as rate [95% confidence interval (CIs)]. The association between degree of stenosis and categories of PSS and quartiles of PSI was tested using linear regression models. Univariable and multivariable Cox proportional hazards models were used to calculate hazard ratios (HRs) with 95% CIs when assessing the association between PSS and PSI and outcomes. Proportional hazards assumptions were tested on basis of Schoenfeld residuals using the *estat phtest* command after fitting a model with *stcox*. We adjusted for confounders in three different models. Model 1: age, sex and systolic blood pressure. Model 2: the same as model 1, degree of stenosis and location of stenosis. Model 3: the same as model 2 and LVMI, LVEF and E/e′-ratio. We adjusted for potential confounders according to significant P trend values in Table 1a–1b, univariable Cox proportional hazards models in Supplemental Table 2, and prior publications investigating PSS [12,13]. Multicollinearity was assessed using *collin* to determine variance inflation factors (VIFs) and tolerance. The mean VIF for model 3 was 1.14 and all values are reported in Supplemental Table 3. Cumulative event rates for each of the endpoints were estimated with the Kaplan-Meier method and compared using log-rank test. Prognostic performance was examined using Harrell's C-statistics in Cox proportional hazards models and the SomersD method. We constructed restricted cubic spline models of incidence rates using Poisson regression models, that were visually inspected to determine if PSI was linearly associated with endpoint events. Based on these models, we conducted a series of sensitivity analyses: low PSI versus intermediate and high values of PSI (Supplemental Table 6). *P*-values < 0.05 in two-sided tests were regarded as statistically significant.

3. Results

Strain measurements were available in 428 patients who experienced ACS and were treated with PCI. The mean age of the study population was

Table 1a
Baseline characteristics according to walls with PSS.

Walls with presence of PSS	No walls (n = 75)	1–2 walls (n = 158)	3–4 walls (n = 136)	5–6 walls (n = 59)	*P* for trend
Clinical characteristics					
Age, years	63 ± 11	65 ± 12	64 ± 13	64 ± 14	0.45
Male, n(%)	56 (75%)	119 (75%)	99 (73%)	40 (68%)	0.34
Systolic blood pressure, mmHg	142 ± 22	135 ± 27	135 ± 25	135 ± 29	0.10
Diastolic blood pressure, mmHg	84 ± 15	82 ± 18	80 ± 15	79 ± 15	0.06
Heart rate, bpm	68 ± 11	74 ± 14	77 ± 16	81 ± 16	<0.001
Prior CAD, n(%)	5 (7%)	15 (10%)	13 (10%)	3 (5%)	0.89
Diabetes, n(%)	4 (5%)	21 (13%)	12 (9%)	2 (3%)	0.43
Dyslipidemia, n(%)	24 (32%)	36 (23%)	29 (21%)	9 (15%)	0.031
Body mass index, kg/m^2	27 ± 5	27 ± 4	26 ± 5	26 ± 4	0.083
Family history of CAD, n(%)	22 (29%)	50 (32%)	49 (29%)	20 (34%)	0.86
Current smoker, n(%)	39 (52%)	60 (38%)	62 (46%)	36 (61%)	0.20
Hospitalization					
Diagnosis					<0.001
• UAP or NSTEMI, n(%)	18 (37%)	32 (20%)	16 (12%)	6 (10%)	
• STEMI, n(%)	47 (63%)	126 (80%)	120 (88%)	53 (90%)	
Stenosis location					0.002
• LAD, n(%)	31 (41%)	61 (39%)	74 (54%)	52 (88%)	
• Cx, n(%)	9 (12%)	31 (20%)	18 (13%)	0 (0%)	
• RCA, n(%)	35 (47%)	66 (42%)	42 (31%)	8 (12%)	
Multivessel CAD, n(%)	7 (9%)	10 (6%)	4 (3%)	2 (3%)	0.042
Degree of stenosis, %	91 ± 15	96 ± 8	97 ± 8	98 ± 6	<0.001
CABG at follow-up, n(%)	0 (0%)	14 (9%)	8 (6%)	2 (3%)	0.69
re-PCI at follow-up, n(%)	4 (5%)	15 (9%)	17 (13%)	5 (9%)	0.23
Echocardiography					
LVEF, %	50 ± 7	43 ± 10	38 ± 11	30 ± 9	<0.001
LVMI, g/m^2	85 ± 17	92 ± 23	94 ± 26	97 ± 23	0.002
E/A ratio	1.1 ± 0.3	1.1 ± 0.4	1.1 ± 0.4	0.9 ± 0.3	0.07
E/e′ ratio	8.8 ± 2.7	10.7 ± 4.0	10.9 ± 4.2	11.7 ± 5.4	<0.001
e′, cm/s	8.8 ± 2.2	7.6 ± 2.2	7.0 ± 2.2	6.6 ± 2.5	<0.001
Deceleration time, ms	187 ± 41	174 ± 50	166 ± 40	147 ± 41	<0.001
Left atrial volume index, mL/m^2	25 ± 8	27 ± 9	25 ± 10	26 ± 7	0.90
GLS, %	−17 ± 2	−14 ± 3	−11 ± 3	−8 ± 3	<0.001
PSI, %	3 ± 2	6 ± 2	8 ± 2	9 ± 1	<0.001
Event rates					
Heart failure, per 1000 patient-years	19 [9; 38]	55 [40; 74]	137 [108; 174]	243 [177; 335]	<0.001
AMI, per 1000 patient-years	11 [5; 27]	20 [13; 32]	27 [18; 42]	28 [14; 53]	0.07
All-cause death, per 1000 patient-years	23 [13; 44]	45 [33; 62]	35 [24; 52]	40 [23; 70]	0.53

Event rates are presented as rate [95% confidence interval].
CAD: coronary artery disease, UAP: unstable angina pectoris, STEMI: ST-segment elevated myocardial infarction, NSTEMI: non ST-segment elevated myocardial infarction, LAD: left anterior descending, Cx: circumflex, RCA: right coronary artery, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, LVEF: left ventricle ejection fraction, LVMI: left ventricle mass index, E: peak transmitral early diastolic inflow velocity, A: peak transmitral late diastolic inflow velocity, e′: peak early diastolic longitudinal mitral annular velocity, GLS: global longitudinal strain, AMI: acute myocardial infarction, PSI: post-systolic index, PSS: post-systolic shortening.

64 years (SD: 12 years) and 73% (n = 314) were men. During the median follow-up time of 3.7 years (IQR 0.3, 5.2 years), 155 (36%) patients were diagnosed with HF, 52 (12%) had an AMI and 87 (20%) died from all causes. The prevalence of PSS in the study population, defined as at least one myocardial segment with $PSI_{segmental} \geq 20\%$, was 82% (n = 353) and the mean PSI was 15.6 ± 15.0%. Patients experiencing HF had a significantly higher number of walls displaying PSS (3.2 ± 1.7 walls vs. 1.9 ± 1.6 walls) and PSI (21.6 ± 16.6% vs. 12.1 ± 14.3%) (P < 0.001 for both).

Patients with more walls exhibiting PSS had a higher heart rate, greater likelihood of STEMI, higher degree of stenosis, more lesions in LAD, lower LVEF and higher incidence of HF (Table 1a). Additionally, parameters of diastolic dysfunction were affected such that E/e′ was increased and DT shortened. The same characteristics applied to increasing quartiles of the PSI (Table 1b). Values of GLS decreased significantly with more walls demonstrating PSS and higher PSI.

3.1. Association with degree of stenosis

Categories of walls with PSS was associated with increasing degree of stenosis (β=1.97, 95%CI 1.01–2.92, P < 0.001 per 1 category increase) and the same applied to quartiles of the PSI (β=1.69, 95%CI 0.89–2.49, P < 0.001 per 1 quartile increase).

3.2. Walls with PSS and outcomes

In unadjusted models per 1 increase in number of walls displaying PSS was significantly associated with HF (HR 1.44 95%CI 1.31–1.57, P < 0.001 per 1 increase) and AMI (HR 1.17 95%CI 1.00–1.36, P = 0.046 per 1 increase). In multivariable models 1–3, increasing number of walls with PSS was an independent predictor of HF (P < 0.001 for all), while no associations with AMI and all-cause death remained significant in all 3 models (Table 2). Stratified according to categories of walls with PSS (1–2 walls; 3–4 walls; 5–6 walls), the association with HF was significant (Fig. 2A), while no relationships were found with AMI and all-cause death (Supplemental Fig. 1A–B). In adjusted models 1–3, the risk of HF increased incrementally with increasing categories of walls exhibiting PSS (Supplemental Table 4). A sensitivity analysis revealed that PSS was a significant predictor of the composite endpoint (consisting of: incident HF, AMI and call-cause death) in a univariable model (HR 1.31 95%CI 1.22–1.41, P < 0.001 per 1 wall increase) and in a fully adjusted model (HR 1.20 95%CI 1.07–1.35, P = 0.001 per 1 wall increase).

3.3. PSI and outcome

Increasing PSI was associated with increased risk of HF and all-cause death, however, only the association with HF remained significant in all

Table 1b
Baseline characteristics according to quartiles of PSI.

Quartiles of PSI	1st quartile (n = 107)	2nd quartile (n = 107)	3rd quartile (n = 107)	4th quartile (n = 107)	*P* for trend
PSI range, %	[0.0–5.1]	[5.2–9.7]	[9.8–20.5]	[20.6–100.0]	
Clinical characteristics					
Age, years	63 ± 11	65 ± 12	63 ± 12	65 ± 14	0.40
Male, n(%)	86 (80%)	77 (72%)	78 (73%)	73 (68%)	0.06
Systolic blood pressure, mmHg	139 ± 21	137 ± 28	139 ± 28	129 ± 27	0.018
Diastolic blood pressure, mmHg	83 ± 16	81 ± 19	81 ± 14	79 ± 16	0.048
Heart rate, bpm	68 ± 11	72 ± 14	73 ± 13	85 ± 17	<0.001
Prior CAD, n(%)	9 (8%)	8 (8%)	13 (12%)	6 (6%)	0.76
Diabetes, n(%)	9 (8%)	9 (8%)	14 (13%)	7 (7%)	0.94
Dyslipidemia, n(%)	33 (31%)	22 (21%)	23 (22%)	20 (19%)	0.051
Body mass index, kg/m^2	27 ± 4	27 ± 5	27 ± 4	25 ± 5	0.050
Family history of CAD, n(%)	34 (32%)	28 (26%)	40 (37%)	29 (27%)	0.89
Current smoker, n(%)	53 (50%)	44 (41%)	41 (38%)	59 (55%)	0.52
Hospitalization					
Diagnosis					
• UAP or NSTEMI, n(%)	34 (32%)	18 (17%)	21 (20%)	9 (8%)	<0.001
• STEMI, n(%)	73 (68%)	89 (83%)	86 (80%)	98 (92%)	
Stenosis location					<0.001
• LAD, n(%)	43 (40%)	42 (39%)	53 (50%)	80 (75%)	
• Cx, n(%)	15 (14%)	16 (15%)	20 (19%)	7 (7%)	
• RCA, n(%)	49 (46%)	49 (46%)	34 (32%)	18 (17%)	
Multivessel CAD, n(%)	8 (7%)	8 (8%)	3 (3%)	4 (4%)	0.10
Degree of stenosis, %	93 ± 13	95 ± 9	97 ± 6	97 ± 7	<0.001
CABG at follow-up, n(%)	4 (4%)	10 (9%)	7 (7%)	3 (3%)	0.57
re-PCI at follow-up, n(%)	6 (6%)	14 (13%)	8 (8%)	12 (11%)	0.37
Echocardiography					
LVEF, %	49 ± 8	46 ± 9	40 ± 9	30 ± 9	<0.001
LVMI, g/m^2	87 ± 17	88 ± 23	96 ± 23	97 ± 27	<0.001
E/A ratio	1.1 ± 0.3	1.1 ± 0.4	1.0 ± 0.4	1.1 ± 0.4	0.57
E/e′ ratio	8.9 ± 2.5	10.7 ± 3.8	11.1 ± 4.1	11.8 ± 5.3	<0.001
e′, cm/s	8.6 ± 2.1	7.7 ± 2.3	6.8 ± 2.0	6.7 ± 2.5	<0.001
Deceleration time, ms	184 ± 41	179 ± 53	170 ± 40	146 ± 38	<0.001
Left atrial volume index, mL/m^2	26 ± 8	26 ± 9	26 ± 11	25 ± 8	0.58
GLS, %	−17 ± 2	−14 ± 3	−12 ± 2	−8 ± 3	<0.001
Event rates					
Heart failure, per 1000 patient-years	20 [11; 35]	63 [45; 90]	112 [85; 149]	207 [161; 265]	<0.001
AMI, per 1000 patient-years	15 [8; 28]	24 [14; 40]	20 [11; 35]	30 [19; 49]	0.15
All-cause death, per 1000 patient-years	21 [12; 37]	43 [29; 64]	24 [14; 40]	66 [47; 93]	0.004

Event rates are presented as rate [95% confidence interval].
CAD: coronary artery disease, UAP: unstable angina pectoris, STEMI: ST-segment elevated myocardial infarction, NSTEMI: non ST-segment elevated myocardial infarction, LAD: left anterior descending, Cx: circumflex, RCA: right coronary artery, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, LVEF: left ventricle ejection fraction, LVMI: left ventricle mass index, E: peak transmitral early diastolic inflow velocity, A: peak transmitral late diastolic inflow velocity, e′: peak early diastolic longitudinal mitral annular velocity, GLS: global longitudinal strain, AMI: acute myocardial infarction, PSI: post-systolic index.

of the adjusted models (Table 2). In both univariable (Fig. 2B) and multivariable models, quartiles of PSI yielded independent and incremental prognostic information on the risk of HF (Supplemental Table 5). In the fully adjusted model, the risk of HF was three-fold increased in the 4th quartile (HR 3.53 95%CI 1.57–7.96, P = 0.002). In univariable models, quartiles of PSI were associated with all-cause death, but not AMI (Supplemental Fig. 2A–B). However, in the fully adjusted model no association was found with all-cause death (Supplemental Table 5).

The association between PSI and HF was linear (Fig. 2C), while relationships with AMI and all-cause death were of non-linear character. In a series of sensitivity analyses no associations with AMI and all-cause death remained significant in the adjusted models (Supplemental Table 6). A sensitivity analysis showed that the PSI was a predictor of the composite endpoint in both a univariable (HR 1.90 95%CI 1.64–2.21, P < 0.001 per 1% increase) and a fully adjusted model (HR 1.53 95%CI 1.21–1.94, P < 0.001 per 1% increase).

3.4. Heart failure: comparison with conventional echocardiographic measurements

In terms of prognostic performance for HF, number of walls with PSS had a lower C-statistics as compared to GLS (C-stat 0.681 (95%CI 0.642–0.721) vs. C-stat 0.715 (95%CI 0.678–0.754), P = 0.093) but the difference was non-significant. The same applied to PSI and GLS (C-stat 0.697 (95%CI 0.657–0.737) vs. C-stat 0.715 (95%CI 0.678–0.754), P = 0.24). Adding number of walls with PSS to conventional echocardiographic risk markers, including LVEF, LVMI, E, DT and LAVI, significantly improved the prognostic performance (C-stat 0.721 (95% CI 0.674–0.768) vs. C-stat 0.683 (95%CI 0.632–0.734), P = 0.044). When PSI was added to the same parameters we also found a significant increase in prognostic performance (C-stat 0.720 (95%CI 0.674–0.766) vs. C-stat 0.683 (95%CI 0.632–0.734), P = 0.048). With regard to HF, unadjusted HRs for echocardiographic measurements are displayed in Supplemental Table 2.

4. Discussion

Our study demonstrates that in patients suffering from ACS, information on PSS obtained after revascularization provides independent prognostic information on the risk of HF. We found no associations between PSS and AMI or all-cause death. To the authors' knowledge no study has examined the prognostic yield of PSS on adverse cardiovascular events in the setting of ACS treated with PCI.

Post-systolic shortening in ischemia has previously been examined in both experimental and clinical studies. Brown et al. demonstrated how PSS in animals, exposed to coronary artery occlusion, predicted systolic recovery immediately after reperfusion [14]. Later, this group described that PSS also predicts recovery of systolic function three weeks after reperfusion [15]. These findings were substantiated and confirmed in patients by Hosokawa et al. [6]. Recently, one study evaluated PSS before and after revascularization in NSTEMI patients, and demonstrated that a high degree of PSS after PCI was significantly associated with decreased improvement in strain at three months' follow-up [7]. Our results extend on those from previous studies that have indicated PSS relates to LV recovery.

Although the mechanism responsible for PSS is unclear, the delayed systolic contraction is thought to arise from dysfunctional myocardial fibers [16]. When the number of walls displaying PSS increases, this indicates a greater amount of dysfunctional myocardial segments. Therefore, the number of walls with PSS reflect the magnitude of myocardial segments prone to impaired recovery. Based on our findings, PSS further provides an indirect estimate of the long-term recovery and the likelihood of developing HF. This hypothesis is strengthened by the fact, that PSS only predicted HF at follow-up and none of the other cardiovascular events. The close association with HF was also confirmed in a prior study from our group, that examined patients with STEMI who were treated with PCI [8]. Furthermore, we hypothesize that when the left ventricle shortens during the diastole, as indicated by PSS, this contributes to a greater end-diastolic pressure and a decreased LV filling pressure, which eventually can lead to HF. This hypothesis is supported by the fact that we found PSS to be strongly associated with measurements of diastolic dysfunction (increased E/e′ and decreased e′, DT). In contrast to other studies, that argued that PSS had to be assessed before reperfusion in order to determine recovery, our results indicate that only one examination of PSS, namely after revascularization, may be sufficient to determine the long-term recovery and prognosis.

The degree of PSI was significantly increased in patients with higher degrees of coronary artery stenosis, and furthermore, the highest quartile of PSI was also associated with the greatest risk of HF. These findings have two implications. First, we argue that PSS characterizes the ischemic burden in the myocardium, which is in line with previous studies [16,17]. Second, we propose that the amount of impaired LV myocardial fibers is directly related to the magnitude of this phenomenon, as displayed by the incrementally increasing risk of HF.

In patients suffering from myocardial ischemia, information about potential recovery and prognosis is scarce in the clinical setting, albeit it is of critical value for risk stratification and intensive monitoring. Long-term risk assessment before discharge consists of routine echocardiography,

Table 2
Survival analyses for walls with post-systolic shortening (per 1 increase in number of walls) and the post-systolic index (per 1% increase).

	HF Hazard ratio (95%CI)	*P* value	AMI Hazard ratio (95%CI)	*P* value	All-cause death Hazard ratio (95%CI)	*P* value
PSS per 1 increase in number of walls						
Unadjusted	1.44 (1.31–1.57) C-stat 0.68	<0.001	1.17 (1.00–1.36) C-stat 0.57	0.046	1.06 (0.94–1.19) C-stat 0.59	0.35
Model 1	1.45 (1.32–1.59)	<0.001	1.18 (1.01–1.37)	0.039	1.04 (0.92–1.17)	0.50
Model 2	1.40 (1.27–1.55)	<0.001	1.20 (1.02–1.43)	0.031	1.01 (0.88–1.15)	0.91
Model 3	1.28 (1.12–1.46)	<0.001	1.19 (0.96–1.48)	0.12	0.92 (0.76–1.11)	0.39
PSI per 1% increase						
Unadjusted	1.96 (1.65–2.32) C-stat 0.70	<0.001	1.15 (0.87–1.51) C-stat 0.58	0.32	1.60 (1.27–2.03) C-stat 0.51	<0.001
Model 1	2.02 (1.69–2.40)	<0.001	1.17 (0.88–1.54)	0.27	1.43 (1.14–1.79)	0.002
Model 2	1.90 (1.57–2.29)	<0.001	1.19 (0.88–1.61)	0.25	1.45 (1.12–1.86)	0.004
Model 3	1.61 (1.21–2.12)	0.001	1.22 (0.79–1.88)	0.37	1.16 (0.79–1.71)	0.45

Model 1 adjusted for age, sex, and systolic blood pressure. Model 2 adjusted for model 1, degree of stenosis and location of stenosis. Model 3 adjusted for model 2, left ventricular mass index, left ventricular ejection fraction and E/e′-ratio.
PSI data was log-transformed.
HF: heart failure, AMI: acute myocardial infarction, PSI: post-systolic index, PSS: post-systolic shortening.

including assessment of LVEF, which is a key prognostic factor [18]. Although conventional echocardiographic measurements are thoroughly validated parameters for prognosis, they can be suboptimal measures, as they can be preserved even when the myocardium is damaged. In our analyses patients in the 2nd quartile of PSI had an LVEF of 46 ± 9% and a two-fold increased risk of HF in adjusted models. In addition to conventional echocardiographic measurements, we encourage that assessment of PSS by STE should be considered in the clinical risk evaluation, as it provides a quick and non-invasive tool for determining who may benefit from extended control programs and may represent a potential future treatment target.

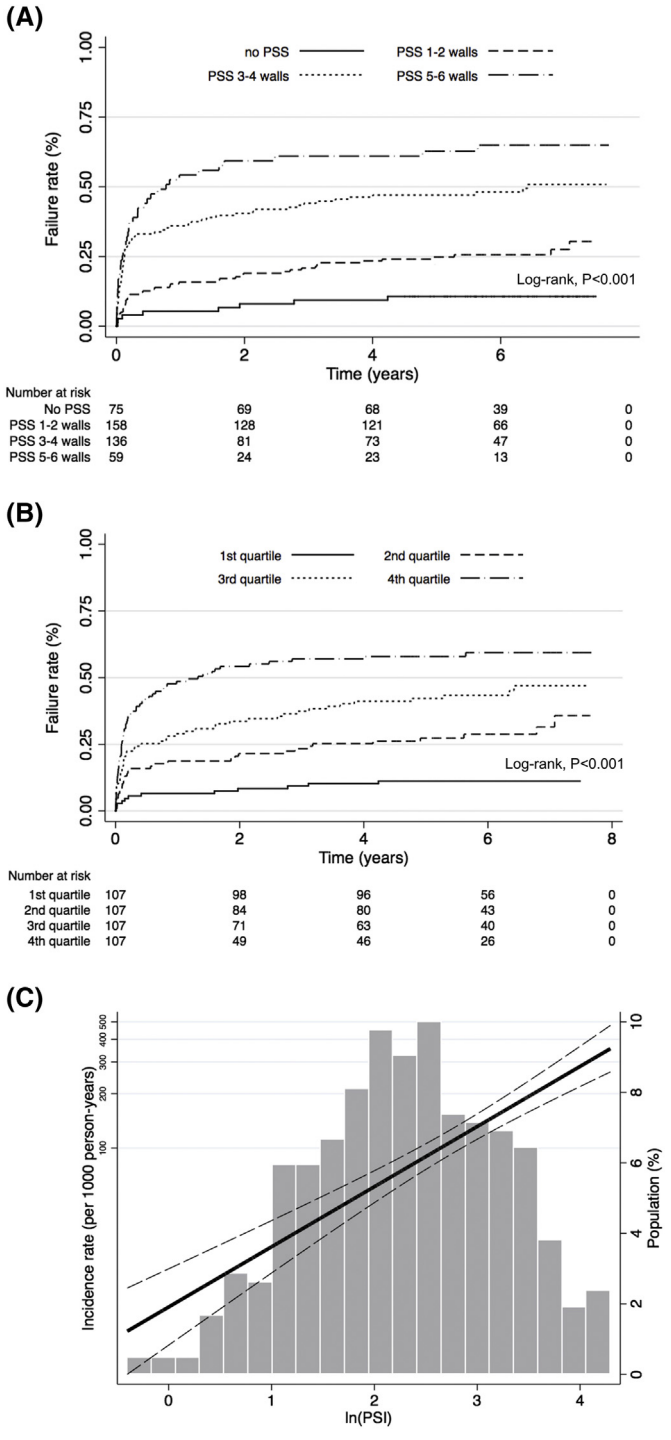

Fig. 2. A–C: Association between walls with post-systolic shortening (PSS), the post-systolic index (PSI) and the endpoint: heart failure. Kaplan Meier failure curves with (A) patients stratified according to categories of walls displaying PSS: no walls, 1–2 walls, 3–4 walls and 5–6 walls and (B) patients stratified according to quartiles of PSI. (C) Cubic spline plot of the association between PSI, assessed as ln(PSI), and the incidence rate of heart failure per 1000 person-years. Full black and dotted black lines show unadjusted incidence rate with 95%CI for increasing values of ln(PSI) and the risk of heart failure.

4.1. Strengths and limitations

The prognostic value of PSS has previously been investigated in STEMI patients [8], and the relationship with systolic recovery in a NSTEMI population [7,19]. In comparison, we investigated a more representative group of ischemic diagnoses, hence providing a more clinically reliable measure on the systolic recovery after ischemia. In our analyses we applied present criteria for differing between pathological and physiological PSS, and additionally, we assessed PSI as a continuous variable [13]. Both ways of assessing PSS yielded independent and significant associations with HF, reinforcing the significance of PSS with regard to systolic recovery. Diagnoses retrieved from the Danish National Patient Registry have been showed to be highly accurate when comparing these with medical records [20].

Unfortunately, no information was available on patient medication during follow-up or renal function. We recognize, that any medications affecting cardiac and renal function at baseline may represent potential confounders for heart disease, and in particular affect the risk of HF, thereby underlining how these parameters could have impacted our results. Our multivariable models are exposed to overfitting due to the low number of events, however, this may be acceptable when controlling for confounders as opposed to building prediction models [21]. Presence of PSS can be assessed by other methods, e.g. tissue Doppler imaging, however, we only examined PSS by speckle tracking in this study. Follow-up echocardiograms in all patients could have provided us with additional information, as we would then have been able to determine the relative change in PSS over time. Unfortunately, follow-up echocardiograms were not available. Patients with lower LVEF following ACS could potentially have a higher risk of developing subsequent HF at follow-up, and moreover, patients with lower LVEF are likely more easy to diagnose with HF. This could potentially have impacted our results. We examined the prognostic performance of different models that included echocardiographic and PSS parameters. However, these models and the potential benefit of assessing PSS should be validated in future and larger cohort studies.

5. Conclusion

Our findings demonstrate that PSS assessed following successful revascularization in patients with ACS is a strong and independent measure on the risk of HF but not on AMI or all-cause death. Our findings suggest that PSS is a potential marker of long-term recovery of LV function following ACS, however, additional studies are required to confirm this hypothesis.

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Disclosures

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.106.

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