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Postsystolic Shortening by Speckle Tracking Echocardiography Is an Independent Predictor of Cardiovascular Events and Mortality in the General Population

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Background—Postsystolic shortening (PSS) has been proposed as a novel marker of contractile dysfunction in the myocardium. Our objective was to assess the prognostic potential of PSS on cardiovascular events and death in the general population.

Methods and Results—The study design consisted of a prospective cohort study of 1296 low-risk participants from the general population, who were examined by speckle tracking echocardiography. The primary end point was the composite of heart failure, myocardial infarction, and cardiovascular death, defined as major adverse cardiovascular events (MACEs). The secondary end point was all-cause death. The postsystolic index (PSI) was defined as follows: [(maximum strain in cardiac cycle−peak systolic strain)/ (maximum strain in cardiac cycle)]×100. PSS was regarded as present if PSI >20%. During a median follow-up of 11 years, 149 participants (12%) were diagnosed as having MACEs and 236 participants (18%) died. Increasing number of walls with PSS predicted both end points, an association that persisted after adjustment for age, sex, estimated glomerular filtration rate, global longitudinal strain, hypertension, heart rate, left ventricular ejection fraction, LV mass index, pro-B-type natriuretic peptide, previous ischemic heart disease, systolic blood pressure, average peak early diastolic longitudinal mitral annular velocity (e′), ratio between peak transmitral early and late diastolic inflow velocity (E/A), and left atrial volume index: MACEs (hazard ratio, 1.35; 95% confidence interval, 1.09−1.67; P=0.006 per 1 increase in walls displaying PSS) and death (hazard ratio, 1.30; 95% confidence interval, 1.08−1.57; P=0.006 per 1 increase in walls displaying PSS). The strongest predictor of end points was ≥2 walls exhibiting PSS. The PSI also predicted increased risk of the end points, and the associations remained significant in multivariable models: MACEs (per 1% increase in PSI: hazard ratio, 1.18; 95% confidence interval, 1.02−1.36; P=0.024) and death (per 1% increase in PSI: hazard ratio, 1.18; 95% confidence interval, 1.05−1.33; P=0.005).

Conclusions—Presence of PSS in the general population provides independent and long-term prognostic information on the occurrence of MACEs and death. (***J Am Heart Assoc***. 2018;7:e008367. DOI: 10.1161/JAHA.117.008367.)

Key Words: deformation • population • postsystolic shortening • prognosis • speckle tracking echocardiography • survival

Cardiac health continues to be a global burden, and risk stratification of patients with early stages of cardiovascular disease is of increasing importance.[1] To address this issue, new echocardiographic modalities, like speckle tracking echocardiography (STE), have emerged in recent years. Quantitative assessment of longitudinal deformation measures and myocardial velocity have allowed identification of even subtle changes in the contractile function, such as postsystolic shortening (PSS). PSS is defined as late systolic shortening appearing after aortic valve closure (AVC), and it occurs in both healthy individuals and in patients experiencing cardiovascular disease.[2–4] Assessment of PSS has been reported useful for detection of acute ischemia and superior to traditional parameters, such as peak systolic strain and wall thickening.[3,5–7] In the setting of acute ischemia, PSS represents regional contractile dysfunction. An experimental study by Asanuma et al[8] showed that PSS persisted after brief periods of ischemia, reflecting a state of systolic stunning that could be used to detect ischemic memory. In addition, PSS has been evaluated in clinical studies, suggesting it as a marker of systolic recovery after an ischemic event.[9,10] Although PSS has been reported to be

Clinical Perspective

What Is New?

- This study shows that postsystolic shortening by speckle tracking echocardiography is a predictor of major adverse cardiovascular events and death in the general population.
- Postsystolic shortening remained an independent risk predictor after adjustment for diastolic and systolic echocardiographic measurements.

What Are the Clinical Implications?

- Presence of postsystolic shortening may be assessed both categorically and continuously and could lead to changes in risk stratification, therapy, or follow-up.
- Easy identification of postsystolic shortening should encourage its use for long-term risk assessment in low-risk individuals.

present in approximately one third of all myocardial segments in healthy individuals,[4] the significance and prognostic value of PSS in the general population remains unexplored (Figure 1). It is the aim of this study to investigate the prognostic potential of PSS on occurrence of major adverse cardiovascular events (MACEs) and death in low-risk individuals.

Methods

Patients and Health Examination

This study included all patients examined in the 4th Copenhagen City Heart Study from January 2001 to December 2003, who had a detailed echocardiographic examination performed. The Copenhagen City Heart Study is a longitudinal cohort study on participants from Copenhagen, Denmark, that assesses cardiovascular diseases, risk factors, and health behavior. Participants were prospectively enrolled in the present study. If a participant underwent an echocardiographic health examination, this was independent of the participant's current health status and risk factors. The study protocol was approved by the local scientific committee and complied with the 2nd Declaration of Helsinki. All participants gave written informed consent before examination. Participants with prevalent heart failure (*International Classification of Diseases, Tenth Revision [ICD-10]* code I50) or atrial fibrillation diagnosed by ECG or during the echocardiographic examination were excluded. Measurements of PSS by STE were available for 1296 participants.

As a part of the physical health examination, all participants answered a self-administered questionnaire. Blood pressure was examined with a sphygmomanometer, and

nonfasting venous blood samples were used for measurement of cholesterol and blood glucose. Quantification of plasma pro-B–type natriuretic peptide was determined in an assay-independent method, and definitions of hypertension, diabetes mellitus, and previous ischemic heart disease have been described in detail previously.[11–15] Because of the sensitive nature of the data collected for this study, requests to access the data set should be sent to the Danish Ministry of Health, the Danish Data Protection Agency, the Steering Committee of the Copenhagen City Heart Study, and the corresponding author.

Echocardiography

Echocardiography was performed with a Vivid 5 ultrasound system (GE Healthcare, Horten, Norway) using a 2.5-MHz transducer. Assessment of conventional 2-dimensional echocardiography and tissue Doppler imaging was performed by trained and experienced sonographers. All data were stored on optical disks and on external hard drives (FireWire, LaCie, France), allowing offline analysis with echocardiographic software (EchoPac, version 2008; GE Medical, Horten, Norway). The investigator was blinded to all other information.

Conventional echocardiography

Conventional echocardiography was performed during resting conditions, and regional function was evaluated by the 16 standard segments model in accordance with recommendations from the American Society of Echocardiography.[16] Analysis of left ventricular (LV) ejection fraction (LVEF) was performed by only 1 examiner on the basis of the wall motion score index. Systolic LV dysfunction was regarded as LVEF <50%. LV mass index was calculated by dividing LV mass by body surface area.

Speckle tracking echocardiography

The 2-dimensional STE was attained from the 3 apical projections: 2-, 3-, and 4-chamber views, with an average of 57 frames per second (SD, 4 frames per second). Six myocardial walls of interest were examined: the septal, lateral, anterior, posterior, inferior, and anteroseptal myocardial walls. Each was divided into subsegments according to the protocol from the American Society of Echocardiography. In the end systole, an automated function defined a region of interest (ROI), thus allowing tracing of the endocardial border. To ensure correct tracking of speckles, the responsible investigator visually assessed the automatically defined ROI. When necessary, the ROI was manually redefined by the investigator. A tracking was regarded as adequate if the following occurred: (1) it covered all of the myocardial wall,
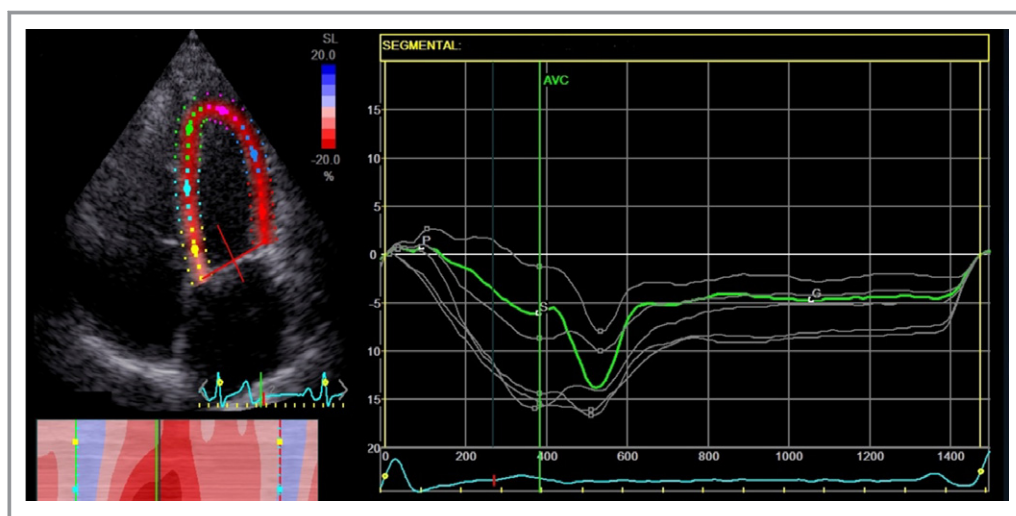
Figure 1. Example of postsystolic shortening (PSS) by speckle tracking echocardiography. Longitudinal strain profiles in 6 segments of the 4-chamber view, where PSS is present in the apical segment (green curve) and exceeds 20% of maximal strain during cardiac cycle. AVC indicates aortic valve closure; and SL, longitudinal strain.

(2) it spanned from the endocardium to the myoepicardial border, and (3) the motion of speckles was visible. If speckles were inadequately visualized, the ROI was manually readjusted. Any tracking not satisfying these requirements or compromised by artefacts/shadows was excluded. When the ROI was set to cover the entire LV, an average value of peak strain from all projections was used to determine global longitudinal strain (GLS). Our laboratory has previously demonstrated good intraobserver and interobserver agreement for speckle tracking calculations.[17] Our laboratory also found good intraobserver and interobserver variability, with only a small bias for PSS (mean difference±1.96 SDs was 0.2±0.95 for intraobserver analysis and −0.04±0.73 for interobserver analysis) and postsystolic index (PSI; mean difference±1.96 SDs was 0.25±0.74 for intraobserver analysis and 0.06±0.56 for interobserver analysis). Data used to calculate PSS were extracted from the 18 myocardial segments. The PSI was derived from the strain curve, as follows: [(maximum strain in cardiac cycle−peak systolic strain)/(maximum strain in cardiac cycle)]×100 (Figure 2). For analysis, the average of PSI from all myocardial walls was used. PSS was assessed qualitatively and regarded as present if PSI was >20%. This cutoff value was based on previous evidence evaluating PSS.[4,18] If 1 segment within a myocardial wall displayed PSS, the wall was categorized as having the presence of PSS. Postsystolic strain was calculated as the absolute difference between maximum strain in the cardiac cycle and systolic strain. Peak postsystolic time was calculated as the time difference between AVC and peak postsystolic strain (Figure 2). Participants with left and right bundle branch block (LBBB/RBBB, respectively) were excluded in a series of sensitivity analyses.

Follow-Up Data

All participants enrolled in the study cohort between 2001 and 2003 were observed until time of event or April 2013. Outcomes were determined from the Danish National Board of Health's National Patient Registry using the *ICD-10*. Follow-up was 100% complete. The primary end point was MACEs, defined as the composite of heart failure, myocardial infarction, and cardiovascular death. Cardiovascular death was defined as *ICD-10* codes I00 to I99. The secondary end point
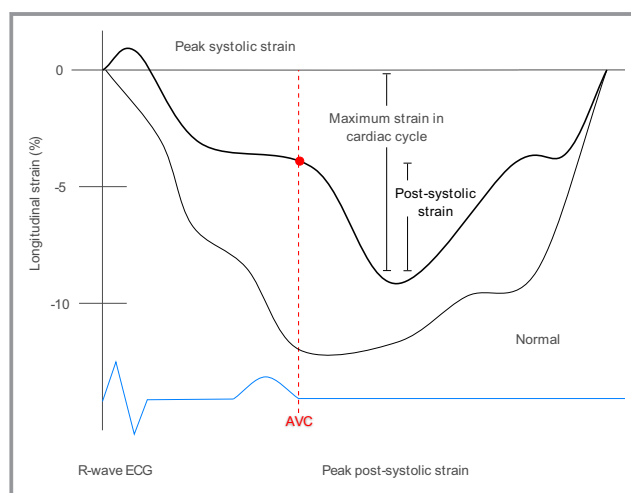

Figure 2. Schematic drawing of measurement of postsystolic index (PSI). Longitudinal strain profile with postsystolic shortening (black curve) and normal strain profile (gray curve). PSI was calculated as follows: [(maximum strain in cardiac cycle−systolic strain)/(maximum strain in cardiac cycle)]×100. AVC indicates aortic valve closure.

was death. All follow-up data were collected from the national Danish Causes of Death Registry.

Statistical Analysis

Baseline clinical data for the population were stratified according to number of walls displaying PSS and tertiles of PSI. Differences between groups for categorical variables were compared using the χ^2 test. *P* value for trend was calculated using linear regression models and the χ^2 trend test. Variables were tested for gaussian distribution using qqplot. The summarized number of segments displaying PSS was calculated and accordingly 3 groups were constructed: (1) no walls with PSS, (2) 1 wall with PSS, and (3) ≥2 walls with PSS. Univariable and multivariable Cox proportional hazards models were used to calculate hazard ratios (HRs). Multivariable Cox proportional hazards models were adjusted for the clinically relevant confounders: age, sex, hypertension, heart rate, LV mass index, LVEF (<50%), GLS, pro-B-type natriuretic peptide, previous ischemic heart disease, systolic blood pressure, left atrial volume index, e′, and E/A. LVEF was adjusted for as a dichotomous variable, with cutoff at 50%. Cumulated event rates were estimated with the Kaplan-Meier method and compared using the log-rank test. Harrell's C-statistics were calculated from univariable Cox proportional hazards models to investigate the prognostic performance of PSS for predicting each end point. PSI was converted to a normal distribution using a logarithmic transformation, and cubic spline plots were made. *P*≤0.05 in 2-sided tests were regarded as statistically significant. All analyses were performed using Stata SE, version 13.1 (StataCorp LP, College Station, TX).

Results

A total of 1323 participants were examined by conventional echocardiography and STE as part of a general health examination. Of these participants, 27 were excluded because of atrial fibrillation or prevalent heart failure. A total of 34 participants (0.03%) had known LBBB or RBBB. Mean age of the study population (n=1296) was 56.9±16.2 years, with a total of 549 men (42.4%). Baseline clinical characteristics are displayed in Table 1. During a median follow-up of 11.0 years (interquartile range, 9.9–11.2 years), 149 participants (11.5%) were diagnosed as having MACEs and 236 participants (18.1%) died.

The prevalence of PSS in the study population was 35.0% (n=453), and a total of 591 myocardial wall segments exhibiting PSS were identified. Participants with presence of PSS were, in general, older, had hypertension, had higher systolic and mean arterial pressures, had lower LVEF and

estimated glomerular filtration rate, had increased LV mass index and body mass index, and were more frequently treated with heart medication (Table 1). In addition, they had a higher incidence of heart failure, cardiovascular death, MACEs, and death. Increasing numbers of walls with PSS were related to a lower GLS, such that participants with no PSS had a mean GLS of −18.4±3.7%, those with 1 wall of PSS had a mean GLS of −17.5±3.6%, and those with ≥2 walls of PSS had a mean GLS of −16.8±3.4% (*P* trend <0.001). Time from AVC until peak PSS increased incrementally with number of walls displaying PSS. In participants with 1 wall versus those with ≥2 walls exhibiting PSS, the median peak time was 29.9 ms versus 45.1 ms after AVC. When the population was stratified in tertiles according to PSI, postsystolic strain and peak postsystolic time increased throughout each tertile (Table 2). Interestingly, no significant difference was found for afterload and GLS between the first and second tertile. Unadjusted HRs (95% confidence intervals [CIs]) for echocardiographic measures (GLS, left atrial volume index, and e′) are displayed in Table 3.

Ordinal Analysis

Per 1 increase in number of walls displaying PSS was associated with a significantly increased risk of MACEs and death (Table 4). In multivariable models, both associations remained significant: MACEs (HR, 1.51; 95% CI, 1.19–1.91; *P*=0.001) and death (HR, 1.24; 95% CI, 1.00–1.54; *P*=0.045). Exclusion of participants with LBBB and RBBB did not alter the results: MACEs (HR, 1.34; 95% CI, 1.08–1.67; *P*=0.009) and death (HR, 1.31; 95% CI, 1.08–1.59; *P*=0.006). Participants were stratified into 3 groups according to number of walls with PSS: (1) no PSS (n=843), 1 wall (n=335), and ≥2 walls (n=118). The risk of MACEs and death increased incrementally with number of walls displaying PSS (log-rank *P*<0.001 for both end points). However, in multivariable models, only presence of PSS in ≥2 walls remained a significant predictor of MACEs (HR, 2.46; 95% CI, 1.48–4.11; *P*=0.001) and death (HR, 1.69; 95% CI, 1.06–2.68; *P*=0.026) (Table 5, Figure 3A and 3B). The results also remained significant when participants with LBBB and RBBB were excluded: MACEs (HR, 1.88; 95% CI, 1.16–3.06; *P*=0.010) and death (HR, 1.83; 95% CI, 1.19–2.79; *P*=0.005). In unadjusted models, PSS had higher HRs for both end points compared with GLS (Table 3). In terms of predictive power for MACEs (C-statistic for PSS versus GLS: 0.59 versus 0.62; *P*=0.243) and death (C-statistic for PSS versus GLS: 0.57 versus 0.56; *P*=0.554), there were no significant differences between PSS and GLS.

Continuous Analysis

PSI showed a nongaussian distribution, which was successfully converted to a gaussian distribution using logarithmic

Table 1. Baseline Clinical Characteristics Stratified According to Number of Walls Displaying PSS

Characteristics	Walls with presence of PSS			P Value for Trend
	No PSS (n=843)	PSS, 1 Wall (n=335)	PSS, ≥2 Walls (n=118)	
Demographics				
Age, y	55.0±16.4	59.5±15.7	64.0±13.0	<0.001
Female sex, n (%)	490 (58.1)	191 (57.0)	66 (55.9)	0.72
Clinical characteristics				
Hypertension, n (%)	282 (33.6)	144 (43.1)	63 (53.4)	<0.001
Mean arterial pressure, mm Hg	94±13	98±13	103±17	<0.001
Diabetes mellitus, n (%)	74 (8.8)	34 (10.3)	14 (11.9)	0.23
Systolic blood pressure, mm Hg	131±22	137±22	143±25	<0.001
Dyslipidemia, n (%)	107 (14.1)	61 (19.9)	18 (16.2)	0.10
BMI, kg/m^2	24.8±3.4	25.6±3.9	25.0±3.3	0.021
eGFR, mL/min per 1.73m^2	77.5±15.9	73.8±15.1	73.8±15.5	<0.001
Smoking, n (%)				
Previous	262 (34.6)	94 (30.7)	38 (33.9)	0.47
Current	251 (32.7)	112 (35.9)	38 (33.9)	0.61
Never	244 (32.2)	100 (32.7)	36 (32.1)	1.00
Heart rate, bpm	65±10	67±11	67±12	<0.001
Heart medication, n (%)	57 (6.8)	42 (12.6)	16 (13.6)	0.001
Pro-BNP, pmol/L	21.5±22.9	22.4±23.6	29.2±32.6	0.007
Previous ischemic heart disease, n (%)	35 (4.2)	19 (5.7)	10 (8.5)	0.043
Echocardiographic characteristics				
PSI, %	1.2±3.0	8.2±2.2	14.9±2.0	<0.001
Postsystolic strain, %	4.7±3.6	18.5±13.4	22.5±10.4	<0.001
Peak postsystolic time, ms	21.1 (10.1–39.4)	29.9 (15.8–49.5)	45.1 (27.9–64.5)	<0.001
GLS, %	−18.4±3.7	−17.5±3.6	−16.8±3.4	<0.001
LVEF, %	59.9±1.1	59.8±1.5	59.1±3.9	<0.001
LVMI, g/m^2	80 (69–94)	84 (72–99)	89 (76–107)	<0.001
LAD, cm	3.4±0.4	3.4±0.4	3.5±0.4	<0.001
Left atrial volume index, mL/m^2	19.3±5.8	19.7±6.3	22.1±7.3	<0.001
e'	7.9±2.7	6.8±2.4	6.2±2.4	<0.001
E/e'	9.3 (7.7–11.7)	10.3 (8.3–13.3)	10.5 (8.5–14.1)	<0.001
E/A	1.1 (0.9–1.4)	1.0 (0.8–1.2)	0.9 (0.8–1.1)	<0.001
Event, n (%)				
Heart failure	44 (5.2)	19 (5.7)	15 (12.7)	0.009
Myocardial infarction	23 (2.7)	14 (4.2)	6 (5.1)	0.094
Cardiovascular death	33 (3.9)	25 (7.5)	16 (13.6)	<0.001
MACEs	75 (8.9)	43 (12.9)	31 (26.3)	<0.001
Death	128 (15.2)	65 (19.4)	43 (36.4)	<0.001

Data are given as mean±SD or median (interquartile range), unless otherwise indicated. BMI indicates body mass index; BNP, B-type natriuretic peptide; bpm, beats per minute; e', average peak early diastolic longitudinal mitral annular velocity; E/A, ratio between peak transmitral early and late diastolic inflow velocity; E/e', ratio between peak transmitral early diastolic inflow velocity and peak early diastolic longitudinal mitral annular velocity; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MACE, major adverse cardiovascular event; PSI, postsystolic index; and PSS, postsystolic shortening.

Table 2. Baseline Clinical Characteristics Stratified According to Tertiles of PSI

Characteristics	PSI in Tertiles			P Value for Trend
	1 (n=432)	2 (n=432)	3 (n=432)	
Demographics				
Age, y	55.1±16.7	54.8±16.1	61.0±15.0	<0.001
Female sex, n (%)	244 (56.5)	257 (59.5)	246 (56.9)	0.56
Clinical characteristics				
Hypertension, n (%)	148 (34.3)	137 (31.9)	204 (47.3)	<0.001
Mean arterial pressure, mm Hg	94±13	94±13	99±14	<0.001
Diabetes mellitus, n (%)	46 (10.6)	30 (7.0)	46 (10.6)	0.99
Systolic blood pressure, mm Hg	131±22	131±23	138±22	<0.001
Dyslipidemia, n (%)	42 (10.9)	75 (19.0)	69 (17.3)	0.02
BMI, kg/m^2	24.6±3.4	24.8±3.5	25.5±3.7	0.001
eGFR, mL/min per 1.73m^2	78.1±16.3	77.4±15.0	73.2±15.5	<0.001
Smoking, n (%)				
Previous	134 (34.8)	134 (34.3)	126 (31.6)	0.59
Current	127 (32.5)	132 (33.4)	142 (35.1)	0.74
Never	124 (32.2)	125 (32.0)	131 (32.8)	0.96
Heart rate, bpm	64±10	65±10	67±11	0.005
Heart medication, n (%)	25 (5.8)	37 (8.6)	53 (12.3)	<0.001
Pro-BNP, pmol/L	22.0±22.9	20.1±22.0	25.2±27.1	0.040
Previous ischemic heart disease, n (%)	13 (3.0)	21 (4.9)	30 (6.9)	0.004
Echocardiographic characteristics				
PSI, %	0.4±2.5	2.5±1.5	11.0±2.0	<0.001
Postsystolic strain, %	3.2±5.6	7.0±3.8	19.3±12.8	<0.001
Peak postsystolic time, ms	15.7 (5.4–34.6)	20.6 (11.1–36.6)	39.0 (22.4–60.1)	<0.001
GLS, %	−18.6±3.7	−18.5±3.6	−17.1±3.6	<0.001
LVEF, %	59.9±0.8	59.9±1.1	59.5±2.5	<0.001
LVMI, g/m^2	79 (69–96)	79 (69–93)	86 (73–101)	<0.001
LAD, cm	3.4±0.3	3.3±0.4	3.5±0.4	0.001
Left atrial volume index, mL/m^2	19.0±5.8	19.4±5.7	20.5±6.9	0.001
e′	8.0±2.9	7.9±2.6	6.6±2.4	<0.001
E/e′	9.2 (7.6–11.6)	9.4 (7.8–11.7)	10.4 (8.5–13.8)	<0.001
E/A	1.1 (0.9–1.5)	1.1 (0.9–1.4)	1.0 (0.8–1.2)	<0.001
Event, n (%)				
Heart failure	22 (5.1)	21 (4.9)	35 (8.1)	0.006
Myocardial infarction	16 (3.7)	7 (1.6)	20 (4.6)	0.44
Cardiovascular death	15 (3.5)	18 (4.2)	41 (9.5)	<0.001
MACEs	40 (9.3)	36 (8.3)	73 (16.9)	<0.001
Death	65 (15.0)	58 (13.4)	113 (26.2)	<0.001

Data are given as mean±SD or median (interquartile range), unless otherwise indicated. BMI indicates body mass index; BNP, B-type natriuretic peptide; bpm, beats per minute; e′, average peak early diastolic longitudinal mitral annular velocity; E/A, ratio between peak transmitral early and late diastolic inflow velocity; E/e′, ratio between peak transmitral early diastolic inflow velocity and peak early diastolic longitudinal mitral annular velocity; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; LAD, left atrial dimension; LVEF, left ventricular ejection shortening; LVMI, left ventricular mass index; MACE, major adverse cardiovascular event; and PSI, postsystolic index.

Table 3. Unadjusted HRs With 95% CIs for MACEs and Death

Echocardiographic Measures Per 1 Increase	MACEs HR (95% CI)	P Value	Death HR (95% CI)	P Value
GLS, %	1.12 (1.08–1.17)	<0.001	1.05 (1.02–1.09)	0.004
LAVI, mL/m^2	1.07 (1.05–1.10)	<0.001	1.06 (1.04–1.08)	<0.001
e′	0.63 (0.58–0.69)	<0.001	0.67 (0.64–0.72)	<0.001

CI indicates confidence interval; e′, average peak early diastolic longitudinal mitral annular velocity; GLS, global longitudinal strain; HR, hazard ratio; LAVI, left atrial volume index; and MACE, major adverse cardiovascular event.

transformation. The incidence of MACEs and death increased incrementally with increasing PSI. Likewise, increasing PSI was associated with significantly increased risk of both end points (Figure 4A and 4B). A continuous analysis of PSI showed that a 1% increase provided prognostic information on both MACEs and death, and the associations remained significant after multivariable adjustment (Table 4). The associations remained significant when participants with LBBB and RBBB were excluded: adjusted MACEs (HR, 1.17; 95% CI, 1.01–1.35; *P*=0.035) and adjusted death (HR, 1.18; 95% CI, 1.05–1.33; *P*=0.007). Stratified according to tertiles of PSI (n=432), participants in the third tertile had a significantly increased risk of MACEs and death (log-rank *P*<0.001 for both end points). After adjustment, those in the third tertile demonstrated a 2-fold increased risk of MACEs (first versus third tertile: HR, 2.18; 95% CI, 1.21–3.91; *P*=0.009) and a little lower risk of death (first versus third tertile: HR, 1.78; 95% CI, 1.11–2.84; *P*=0.017) (Table 5). Exclusion of participants with LBBB and RBBB had only minor impact on the previous results: MACEs (first versus third

tertile: HR, 1.83; 95% CI, 1.05–3.20; *P*=0.033) and death (first versus third tertile: HR, 1.90; 95% CI, 1.21–3.00; *P*=0.005). In comparison with GLS, the PSI maintained higher HRs in unadjusted analyses for both end points (Table 3). For MACEs, the predictive performance was nearly the same (C-statistic for PSI versus GLS: 0.63 versus 0.62; *P*=0.739); however, for death, the PSI had a significantly better performance than GLS (C-statistic for PSI versus GLS: 0.62 versus 0.56; *P*=0.007).

Discussion

In this prospective study of the general population, we demonstrated that PSS assessed by STE provides independent prognostic information on the occurrence of MACEs and death. To the best of our knowledge, no study has addressed the prognostic value of PSS in a low-risk general population.

Previous studies have focused on PSS in the settings of acute ischemia and chronic coronary artery disease,[5,7,8,19,20]

Table 4. Risk of MACEs and Death According to Increasing Number of Walls With PSS and Increasing PSI

Variable	MACEs HR (95% CI)	P Value	Death HR (95% CI)	P Value
No. of walls with PSS				
Unadjusted				
Per 1 increase in number of walls	1.59 (1.34–1.89) (C-statistic, 0.59)	<0.001	1.51 (1.31–1.75) (C-statistic, 0.57)	<0.001
Adjusted*				
Per 1 increase in number of walls	1.51 (1.19–1.91)	0.001	1.24 (1.00–1.54)	0.045
PSI				
Unadjusted				
PSI per 1% increase	1.36 (1.20–1.54) (C-statistic, 0.63)	<0.001	1.33 (1.21–1.47) (C-statistic, 0.62)	<0.001
Adjusted*				
PSI per 1% increase	1.22 (1.04–1.43)	0.014	1.14 (1.00–1.30)	0.044

CI indicates confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; PSI, postsystolic index; and PSS, postsystolic shortening.
*Adjusted for sex, age, hypertension, heart rate, left atrial volume index, left ventricular mass index, ejection fraction, global longitudinal strain, pro-B-type natriuretic peptide, previous ischemic heart disease, systolic blood pressure, average peak early diastolic longitudinal mitral annular velocity (e′), ratio between peak transmitral early and late diastolic inflow velocity (E/A), and estimated glomerular filtration rate.

Table 5. Risk of MACEs and Death According to Grouped Number of Walls With PSS and Tertiles of PSI

Variable	MACEs HR (95% CI)	P Value	Death HR (95% CI)	P Value
No. of walls with PSS				
Unadjusted				
Per 1 increase in category of walls with PSS	1.76 (1.43–2.17) (C-statistic, 0.59)	<0.001	1.56 (1.32–1.86) (C-statistic, 0.57)	<0.001
0 Walls	Reference		Reference	
1 Wall	1.47 (1.01–2.14)	0.044	1.29 (0.96–1.74)	0.094
≥2 Walls	3.31 (2.17–5.03)	<0.001	2.68 (1.90–3.79)	<0.001
Adjusted*				
Per 1 increase in category of walls with PSS	1.54 (1.19–1.99)	0.001	1.24 (0.99–1.55)	0.067
0 Walls	Reference		Reference	
1 Wall	1.32 (0.84–2.11)	0.225	1.02 (0.69–1.50)	0.924
≥2 Walls	2.46 (1.48–4.11)	0.001	1.69 (1.06–2.68)	0.026
Tertiles of PSI				
Unadjusted				
Per 1 increase in tertiles	1.75 (1.40–2.18) (C-statistic, 0.62)	<0.001	1.68 (1.40–2.00) (C-statistic, 0.61)	<0.001
1	Reference		Reference	
2	1.44 (0.87–2.38)	0.151	1.43 (0.96–2.12)	0.075
3	2.89 (1.84–4.54)	<0.001	2.70 (1.88–3.86)	<0.001
Adjusted*				
Per 1 increase in tertiles	1.51 (1.13–2.02)	0.006	1.36 (1.07–1.72)	0.011
1	Reference		Reference	
2	1.27 (0.69–2.33)	0.437	1.14 (0.70–1.87)	0.588
3	2.18 (1.21–3.91)	0.009	1.78 (1.11–2.84)	0.017

CI indicates confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; PSI, postsystolic index; and PSS, postsystolic shortening.

*Adjusted for sex, age, hypertension, heart rate, left atrial volume index, left ventricular mass index, ejection fraction, global longitudinal strain, pro-B-type natriuretic peptide, previous ischemic heart disease, systolic blood pressure, average peak early diastolic longitudinal mitral annular velocity (e′), ratio between peak transmitral early and late diastolic inflow velocity (E/A), and estimated glomerular filtration rate.

where PSS acts as both a marker of ischemic insults and a predictor of systolic recovery. Because of this, only few studies have examined the incidence of PSS among healthy individuals and none have examined the incidence in a low-risk population. No studies have associated PSS with outcome. In this study, we found a prevalence of PSS of 35%, a finding almost similar to that of Voigt et al, who examined healthy participants and found an incidence of 31%.[4] In healthy individuals, physiological PSS is a part of a natural and balanced reshaping process that occurs during the isovolumetric relaxation time. In participants experiencing cardiovascular disease, PSS is believed to occur because of passive elastic recoil caused by heterogeneity between dyskinetic myocardial segments and healthy tissue.[2,21] We used a 20% cutoff value of PSI, as suggested by Voigt et al,[4] to qualitatively differentiate between pathological and physiological PSS. Furthermore, we

assessed PSS continuously using the PSI. Both methods for assessing the prognostic value of PSS were independently associated with outcomes.

By examining the general population, we were able to explore the presence of PSS and outcome at different stages. In the study cohort, we found that increasing number of walls displaying PSS and a high PSI were associated with worse outcome. When PSI was stratified according to tertiles, participants in the second tertile of PSS had, albeit modest, a lower incidence of MACEs and death, a significantly greater postsystolic strain, and longer peak postsystolic time. In the second tertile, mean PSI was 2.5% and conventional echocardiographic measurements (EF, GLS, and LV mass index) were normal. Hence, echocardiographic measures could not be used to differentiate participants in the second tertile from those in the first tertile. In comparison, participants in the third tertile of PSI (mean PSI, 11.0%) had a significantly
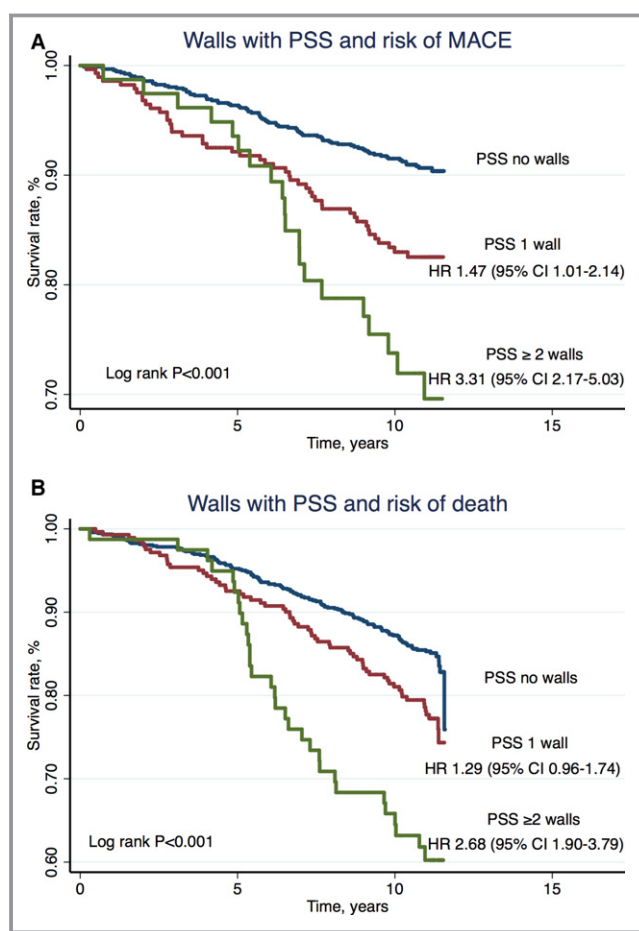
Figure 3. A and B, Kaplan-Meier survival curves with patients stratified according to number of walls displaying postsystolic shortening (PSS): no walls, 1 wall, and ≥2 walls. A, Participants with PSS in ≥2 walls had the highest risk of major adverse cardiovascular events (MACEs) (hazard ratio [HR], 3.31; 95% confidence interval [CI], 2.17–5.03). B, Participants with PSS in ≥2 walls had the highest risk of death (HR, 2.68; 95% CI, 1.90–3.79).

Figure 4. A and B, Cubic spline plots of postsystolic index (PSI). Association between log(PSI) and risk of major adverse cardiovascular events (MACEs) and death in the population. Black and blue lines show unadjusted hazard ratio (HR) with 95% confidence interval for increasing values of ln(PSI). Orange line is HR of 1.0. The histogram shows the distribution of PSI. Increasing ln(PSI) is associated with increased risk of MACEs (A) and increased risk of death (B).

increased incidence of events and a lower survival rate. Previous studies support the hypothesis that PSS is a dichotomous phenomenon that either represents cardiac viability or regional contractility defects.[4,20,22] In contrast to this, our findings suggest that occurrence of PSS should not solely be regarded dichotomous. Instead, it should be regarded as a dynamic and progressive phenomenon that may alter over time in low-risk individuals and, thus, develop from a physiological to a pathological state. We hypothesize when PSS occurs at a low magnitude and with increased postsystolic time it represents active myocardial fibers; however, when PSS gradually develops and exceeds 11% of maximum strain in the cardiac cycle, it's presence is pathologic and associated with increased risk of MACEs and death. Several conditions should be taken into account considering our findings. First, a relative difference exists
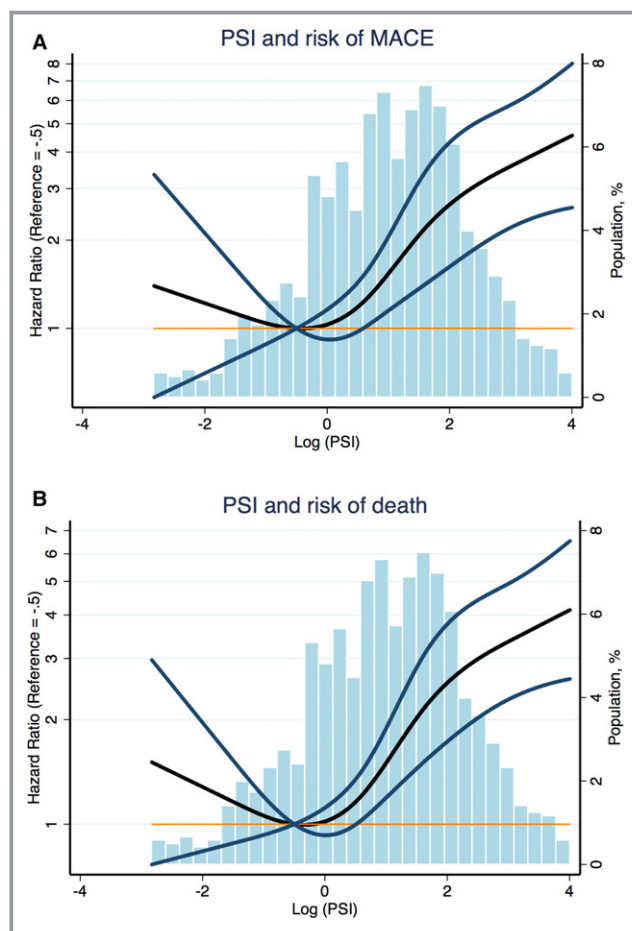
between the current population and previous studies as they did the following: (1) examined patients experiencing known or suspected ischemic heart disease[4,7,20,22–25] or (2) performed animal experiments.[3,26,27] Second, we only assessed longitudinal deformation measurements and not radial thickening, which might have influenced our results.

PSS is a phenomenon that occurs widely in the general population, and differentiation between physiological and pathological PSS is of crucial importance for its use in clinical settings. To fully explore the prognostic potential of PSS in low-risk individuals, a more detailed understanding of the mechanisms causing progression of PSS is needed, thus allowing us, with greater detail, to determine if PSS is derived from viable or dysfunctional myocardial segments. We found that participants with increasing number of walls with PSS had significantly more comorbidity, were older, and had lower

GLS; peak PSS also occurred later in the cardiac cycle in these participants. Because PSS was highly related with both age and comorbidity, this might reduce its predictive value in a low-risk general population because both PSS and comorbidities are linked to cardiovascular events and mortality. Yet, our results demonstrate that PSS remains an independent predictor of both MACEs and death after adjustment for all the aforementioned comorbidities, and the fact that it is easily accessible by STE should add to the identification of this phenomenon in clinical settings.

Strengths and Limitations

The study population is from the Copenhagen City Heart Study, a large community-based cohort involving a homogeneous sample of men and women across different ages with complete follow-up. This is a major strength to the current study. Using STE for assessment was an advantage compared with studies using tissue Doppler imaging,[9] because this method reduced any user-dependent estimation of PSS and is regarded as a more reliable technique for quantifying deformation measurements. However, speckle tracking is a noninvasive technique for assessment of myocardial wall forces; thus, it cannot distinguish active from passive forces or reveal the true cause of myocardial deformation. Bundle branch block is known to be a contributor to occurrence of PSS, explaining why we performed series of sensitivity analyses excluding participants with known LBBB/RBBB. Skulstad et al[27] showed that increasing LV peak systolic and end-diastolic pressures was related to higher occurrence of PSS. To reduce the influence of loading conditions on the prognostic value of PSS, we adjusted for systolic blood pressure and hypertension in our multivariable models.

A limitation to the current study is that we examined the magnitude and peak time of PSS, but we did not assess the total duration of PSS after AVC, the isovolumetric relaxation time. This might have provided additional information on the physiological features of PSS. Data on radial and circumferential deformational measurements were not available, allowing us to only examine longitudinal deformation. Information on these measurements may have added to a greater understanding of the physiological features of PSS. Data on changes in treatment or cardiac interventions during the follow-up were not available. Thus, effect of treatment may have influenced the presence of PSS over time and its association with events. A recent guideline for standardization of deformation imaging highlighted the variability in regional strain measurements.[28] To reduce this variability, we regarded PSS as a global phenomenon. Hence, we assessed the summarized number of walls displaying PSS from all regions, and PSI was calculated as the mean from all myocardial regions. In performing speckle analyses, the width

of the ROI may have influenced occurrence of PSS. We did not keep track of how often the ROI was manually adjusted, nor did we examine the impact of ROI width on PSS.

Conclusion

PSS assessed by STE in a low-risk general population provides novel and independent long-term prognostic information on the risk of MACEs and death. Albeit PSS is associated with increasing comorbidity and age, the easy identification of PSS by STE should encourage its use for long-term risk assessment in individuals with low risk of cardiovascular disease.

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Disclosures

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