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ORIGINAL RESEARCH

Right Ventricular Function Evaluated by Tricuspid Annular Plane Systolic Excursion Predicts Cardiovascular Death in the General Population

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***Background*—**Cardiovascular disease remains a leading cause of death. Right ventricular (RV) function is a strong predictor of outcome in many cardiovascular diseases, but its significance is often neglected. Little is known about the prognostic value of RV systolic function in the general population. Therefore, we aimed to determine the prognostic value of RV systolic function, evaluated by tricuspid annular plane systolic excursion (TAPSE), in predicting cardiovascular death (CVD) in the general population.

***Methods and Results*—**A total of 1039 participants from the general population without heart failure or atrial fibrillation had an echocardiogram performed and TAPSE measured. The end point was CVD. During a median follow-up of 12.7 years (interquartile range, 12.0–12.9 years), 69 participants (6.6%) experienced CVD, whereas 162 participants (15.6%) experienced non-CVD. Decreasing RV systolic function, assessed as TAPSE, was a univariable predictor of CVD (hazard ratio, 1.13; 95% CI, 1.07–1.20; $P<0.001$, per 1-mm decrease). TAPSE remained an independent predictor of CVD after adjusting for clinical and echocardiographic parameters (hazard ratio, 1.08; 95% CI, 1.01–1.15; $P=0.017$, per 1-mm decrease). Furthermore, in net reclassification analysis, decreasing RV systolic function, assessed as TAPSE, significantly improved risk classification with respect to CVD when added to established cardiovascular risk factors from the Systematic Coronary Risk Evaluation chart or a modified version of the American Heart Association/American College of Cardiology Pooled Cohort Equation. Decreasing RV systolic function, assessed as TAPSE, did not predict non-CVD, indicating specificity for CVD.

***Conclusions*—**RV systolic function, as assessed by TAPSE, is associated with CVD in the general population. In the general population, assessment of RV systolic function may provide novel prognostic information about the risk of CVD. **(*J Am Heart Assoc*. 2019;8:e012197. DOI: 10.1161/JAHA.119.012197.)**

Key Words: cardiovascular death • cardiovascular risk • general population • prognosis • right ventricle • right ventricle echocardiography • tricuspid annular plane systolic excursion

To this day, cardiovascular disease remains the leading cause of death.[1] Currently, methods for predicting cardiovascular risk in the general population rely on old and simple risk models.[2] The European Society of Cardiology has, in a recent position statement, emphasized that current risk scores, such as the SCORE risk chart[3] and the American College of Cardiology (ACC)/American Heart Association (AHA) Pooled Cohort Equation,[4] are useful but insufficient for predicting cardiovascular risk in the general population.[5] One size does not fit all. Personalized medicine in cardiology practice can be viewed as a continuum in which new technologies are continuously incorporated into clinical practice. A feasible method of collecting a large amount of personalized information on cardiac structure and function may be echocardiography. However, before this information can be used to personalize risk prediction in the general population, the incremental prognostic value of individual parameters must be thoroughly tested and validated.[2]

The right ventricle (RV) has often been coined "the forgotten chamber."[6] RV dysfunction is an established predictor of morbidity and mortality in both cardiovascular and respiratory diseases, including heart failure (HF),[7]

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Accompanying Tables S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012197

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Clinical Perspective

What Is New?

- No studies have investigated the prognostic value of right ventricular systolic function, assessed as tricuspid annular plane systolic excursion, in a large cohort of individuals from the general population.
- In our study, tricuspid annular plane systolic excursion was an independent predictor of cardiovascular death in individuals from the general population; this was true even in people with normal left ventricular ejection fraction (≥60%).

What Are the Clinical Implications?

- Tricuspid annular plane systolic excursion may facilitate early identification of individuals at high risk of cardiovascular death, allowing for prompt intervention and intensified follow-up.

myocardial infarction,[8] primary pulmonary hypertension,[9] and chronic obstructive pulmonary disease.[10] Chronic lung disease, such as chronic obstructive pulmonary disease, can lead to hypoxemic vasoconstriction and destruction of pulmonary capillary beds, which increases pulmonary circulatory resistance and, thus, RV afterload. Consequently, in patients with chronic obstructive pulmonary disease, RV systolic dysfunction is a marker of poor prognosis.[10] In addition, the RV is also directly affected by the downstream left ventricular (LV) filling pressure as a result of circulatory coupling and RV function is impaired in conditions of diastolic dysfunction, such as in HF with preserved ejection fraction.[11] Diastolic dysfunction is a strong predictor of adverse cardiovascular outcome in the general population.[12] Currently, the prognostic value of RV systolic function, quantified by echocardiography, in predicting cardiovascular death (CVD) and other cardiovascular outcomes in the general population is largely unknown.

This study sought to investigate the prognostic value of an easily obtainable measure of RV systolic function, such as the tricuspid annular plane systolic excursion (TAPSE), in predicting cardiovascular mortality in the general population.

Methods

Data Availability

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Because this study uses data from human subjects, the data and everything pertaining to them are governed by the Danish Data Protection Agency and can only be made available to any additional researchers if a formal request is filed with the Danish Authorities.

Study Sample

The present study sample is an echocardiographic substudy of the CCHS (Copenhagen City Heart Study), a longitudinal cohort study designed to study cardiovascular risk factors. The population has previously been described in detail.[13] The population is based in and around the Copenhagen city area. In the fourth round of examination, participants were allocated for echocardiography in a random manner. At first, 2221 participants had an echocardiogram, including tissue Doppler imaging, performed. For this substudy, 67 participants were excluded because of prevalent HF or atrial fibrillation. Because the echocardiograms were obtained in 2001 to 2003 using a protocol not specifically designed for RV analysis, 1115 participants had to be excluded because of inadequate image quality for measurement of TAPSE. Most of these exclusions were because of the lateral tricuspid annulus area being outside of the imaging plane during part of the cardiac cycle, making tracking of the systolic motion nonfeasible, or because of acoustic shadowing of the lateral tricuspid annulus. A comparison of excluded participants with included participants is available in Table S1. This left 1039 participants for inclusion into the present study.

Ethics

Written consent was collected from all participants, and the study design was approved by a regional scientific ethics committee. Finally, the study complies with the Second Declaration of Helsinki.

General Health Examination

Participants were subject to a general health examination, consisting of a questionnaire and a physical examination. In addition, participants had their lung function assessed by spirometry. The presence of obstructive lung function at baseline was defined as a forced expiratory volume in 1 second (FEV1) divided by the forced vital capacity of <0.7.

Definitions of diabetes mellitus, hypertension, and prevalent ischemic heart disease have previously been described.[13]

Echocardiography

All echocardiograms were obtained using Vivid 5 ultrasound machines (GE Healthcare, Horten, Norway) by 3 experienced sonographers with a 2.5-MHz transducer. All examinations underwent offline analysis by another experienced investigator. This investigator was blinded to all outcome and clinical

data. The offline analysis was done using commercially available software (EchoPac, version 8; GE Healthcare).

Conventional Echocardiography

The wall motion score index was assessed using the 16-segment model and used to calculate the LV ejection fraction (LVEF).[14] TAPSE was measured in the lateral tricuspid annulus from the apical 4-chamber view using an M-mode cursor. LV hypertrophy was defined as directed in current guideliens.[14] Peak early and late diastolic inflow velocities were derived from mitral inflow patterns using pulsed-wave Doppler between the mitral leaflet tips in the apical position. These were used to calculate early/late diastolic inflow velocity and to measure deceleration time of the E-wave.

Color Tissue Doppler Imaging

Color tissue Doppler imaging velocity tracings, with the range gate positioned in the lateral and septal mitral annulus of the 4-chamber view, were obtained. These were used to determine the peak systolic tissue velocity (s′), the peak early diastolic velocity (e′), and the peak late diastolic velocity. Then, the ratio of the E wave/e′ (E/e′) was calculated.

Follow-Up and Outcome

The participants were enrolled in 2001 to 2003. They were followed up until time to death or until October 2014. The end point of this study was CVD. When assessing the outcome of CVD, non-CVD (NCD) was treated as a censoring event. A secondary end point was NCD. When assessing the outcome of NCD, CVD was treated as a censoring event. The Danish National Cause of Death Registry and the Danish National Board of Health's National Patient Registry were used to obtain follow-up data. Follow-up data were retrieved using the *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes. CVD was defined as *ICD-10* codes I00 to I99. NCD was defined as *ICD-10* codes not equal to I00 to I99. Follow-up was 100%.

Statistical Analysis

Statistical analysis was performed using STATA 13.0 for Mac OS. In Table 1, continuous variables, exhibiting gaussian distribution, were compared using the Student *t* test and reported as mean±SD. In the case of a nongaussian distribution, continuous variables were compared using the Wilcoxon rank-sum test and reported as median with interquartile ranges. Proportions were compared using the χ^2 test. In Table 2, linear regression of means was used to analyze trend over tertiles of TAPSE. In Table 3, univariable and multivariable Cox regressions were used to assess the prognostic value of TAPSE in predicting CVD and NCD. The number of events per adjusting variable was set to ≈5,[15] leaving room for a maximum of 14 adjusting variables in the final multivariable model (69 CVDs at follow-up). Statistical significance was defined as $P \leq 0.05$ in 2-sided *t* tests. In the Figure, Poisson regression, using robust standard errors to control for overdispersion, was used to estimate incidence rates of CVD as a function of TAPSE. In Table S2, multivariable linear regression analysis, adjusted for established cardiovascular risk factors and comorbidities, was used to determine associations between TAPSE and other echocardiographic parameters (Table S2). In Table S3, net reclassification improvement[16] analysis was used to assess the incremental prognostic value of TAPSE when added to established cardiovascular risk factors in predicting CVD (Table S3). In these analyses, we chose to assess the incremental prognostic value of adding TAPSE to risk factors from the SCORE risk chart[3] because this model is used in daily clinical practice in Denmark. In addition, we also considered the AHA/ACC Pooled Cohort equation[4] (excluding race because the inhabitants of Denmark are mainly white) because this model is recommended in the new 2017 ACC/AHA guidelines on the management of hypertension[17] and also the Framingham risk score because of its widespread use and credibility.[18]

Results

Follow-Up and Outcome

The median follow-up time was 12.7 years (interquartile range, 12.0–12.9 years), and follow-up was 100%. The primary end point of CVD was reached by 69 participants (6.6%). A total of 162 participants reached the secondary end point of NCD (15.6%).

Baseline Characteristics, According to Exclusion Status

Excluded participants were older, were more hypertensive, and had a larger body mass index (Table S1). They were also more likely to be men and to have higher heart rates (Table S1).

Baseline Characteristics of the Population, According to CVD

Participants who experienced CVD were older and more hypertensive (Table 1). Furthermore, participants who experienced CVD displayed a higher prevalence of comorbidities (Table 1). With regard to echocardiography, participants who

Table 1. Population Stratified According to CVD and NCD

Variable	All Participants	No CVD	CVD	*P* Value*	NCD	*P* Value†
Demographics						
No.	1039	970	69		162	
Age, y	57.3 (16.0)	56.0 (15.7)	75.2 (8.3)	<0.001	70.7 (11.2)	<0.001
Men	416 (40.0)	382 (39.4)	34 (49.3)	0.11	76 (46.9)	0.042
Clinical characteristics						
Systolic blood pressure, mm Hg	133.6 (22.9)	132.3 (22.3)	152.8 (23.3)	<0.001	144.6 (21.5)	<0.001
Diastolic blood pressure, mm Hg	77.6 (12.3)	77.3 (11.9)	82.5 (16.1)	<0.001	78.0 (11.6)	0.72
Pulse pressure, mm Hg	55.9 (18.2)	54.9 (17.4)	70.7 (23.1)	<0.001	66.7 (18.3)	<0.001
Mean arterial pressure, mm Hg	96.1 (14.2)	95.4 (13.9)	105.8 (15.6)	<0.001	100.0 (13.)	<0.001
Hypertension	392 (39.0)	341 (36.3)	51 (79.7)	<0.001	105 (65.6)	<0.001
Smoking	352 (35.4)	330 (35.5)	22 (33.8)	0.79	67 (42.1)	0.049
Body mass index, kg/m^2	25.4 (3.9)	25.3 (3.8)	26.6 (4.7)	0.008	25.7 (3.9)	0.39
Diabetes mellitus	96 (9.6)	85 (9.0)	11 (17.5)	0.028	22 (13.8)	0.050
Heart rate, BPM	67 (1)	66 (11)	68 (12)	0.45	69 (12)	<0.001
Ischemic heart disease	45 (4.5)	40 (4.3)	5 (7.8)	0.02	17 (10.6)	0.008
Acute myocardial infarction	16 (1.6)	14 (1.5)	2 (3.1)	0.31	9 (5.6)	0.009
FEV1, L	2.81 (0.98)	2.87 (0.97)	2.04 (0.65)	<0.001	2.16 (0.75)	<0.001
FVC, L	3.65 (1.17)	3.71 (1.17)	2.81 (0.81)	<0.001	2.98 (0.90)	<0.001
FEV1/FVC	0.77 (0.08)	0.77 (0.08)	0.73 (0.11)	<0.001	0.72 (0.10)	<0.001
Obstructive lung function	167 (16.1)	146 (15.1)	21 (30.4)	<0.001	50 (31.0)	<0.001
Laboratory work						
Total cholesterol, mmol/L	5.58 (1.16)	5.56 (1.16)	5.83 (1.06)	0.07	5.75 (0.11)	0.052
Plasma pro-BNP, pmol/L	15 (7–28)	15 (7–26)	33 (14–64)	<0.001	20.5 (8.5–40)	<0.001
eGFR, mL/min per 1.73 m^2	73 (20)	74 (20)	65 (21)	<0.001	68 (21)	<0.001
Echocardiography						
TAPSE, mm	26 (5)	27 (5)	24 (5)	0.001	26 (4)	0.004
LVEF, %	59.8 (1.3)	59.8 (1.2)	59.4 (1.9)	0.048	59.5 (2.2)	0.01
LV hypertrophy	248 (23.9)	218 (22.5)	30 (43.5)	<0.001	60 (37.0)	<0.001
LVIDd, cm	4.8 (0.5)	4.8 (0.5)	4.7 (0.5)	0.36	4.6 (0.6)	<0.001
LVMI, g/m^2	84.3 (20.7)	83.1 (19.3)	102.4 (29.9)	<0.001	88.7 (20.3)	0.011
Left atrium dimension, cm	3.4 (.4)	3.4 (0.4)	3.6 (0.4)	<0.001	3.5 (0.4)	0.003
E/e′	10.7 (4.2)	10.4 (4.0)	14.9 (50)	<0.001	12.8 (5)	<0.001
E/A	1.12 (0.43)	1.13 (0.43)	0.89 (0.35)	<0.001	0.91 (0.37)	<0.001
Deceleration time, ms	166 (41)	165 (39)	186 (56)	<0.001	175 (51)	0.005
s′, cm/s	6.0 (1.2)	6.0 (1.2)	5.3 (1.2)	<0.001	5.5 (1.1)	<0.001
e′, cm/s	7.4 (2.7)	7.6 (2.6)	4.8 (1.5)	<0.001	5.7 (1.9)	<0.001
a′, cm/s	6.5 (1.9)	6.5 (1.9)	6.8 (1.9)	0.20	7.3 (1.7)	<0.001

Data are given as number, number (percentage), or mean (SD). a′ Indicates peak late diastolic velocity; BPM, beats per minute; CVD, cardiovascular death; e′, peak early diastolic velocity; E/A, early/late diastolic inflow velocity; E/e′, ratio of the E wave/e′; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LV, left ventricular; LVEF, LV ejection fraction; LVIDd, LV inner diameter at end diastole; LVMI, LV mass index; NCD, non-CVD; pro-BNP, pro-B-type natriuretic peptide; s′, peak systolic tissue velocity; TAPSE, tricuspid annular plane systolic excursion.

*Comparing participants experiencing CVD with participants who did not experience CVD.

†Comparing participants who experienced death from noncardiovascular causes with participants who did not experience death from noncardiovascular causes.

Table 2. Population Stratified According to Tertiles of TAPSE

Variable	All Participants	Worse	→	Better	*P* Value for Trend
		First Tertile, TAPSE <24 mm	Second Tertile, 24 mm < TAPSE <28 mm	Third Tertile, TAPSE >28 mm	
Demographics					
No.	1039	349	347	343	
Age, y	57.3 (16.0)	61.0 (16.1)	56.0 (15.6)	54.9 (15.8)	<0.001
Men	416 (40.0)	137 (39.3)	130 (38.0)	149 (42.8)	0.34
Clinical characteristics					
Systolic blood pressure, mm Hg	133.6 (22.9)	135.9 (22.9)	132.9 (23.5)	132.1 (22.2)	0.029
Diastolic blood pressure, mm Hg	77.6 (12.3)	78.6 (12.3)	77.2 (11.6)	77.2 (12.9)	0.14
Pulse pressure, mm Hg	55.9 (18.2)	57.2 (18.5)	55.8 (19.5)	54.8 (16.6)	0.09
Mean arterial pressure, mm Hg	96.1 (14.2)	97.4 (14.2314)	95.6 (13.7)	95.2 (14.6)	0.046
Hypertension	392 (39.0)	148 (44.4)	131 (39.3)	112 (33.4)	0.003
Smoking	352 (35.4)	125 (37.8)	114 (34.9)	113 (33.5)	0.25
Body mass index, kg/m^2	25.4 (3.9)	25.3 (4.0)	25.5 (4.0)	25.5 (3.7)	0.32
Diabetes mellitus	96 (9.6)	33 (9.9)	44 (13.3)	19 (5.6)	0.06
Heart rate, BPM	67 (1)	69 (12)	66 (11)	65 (11)	<0.001
Ischemic heart disease	45 (4.5)	28 (8.4)	4 (1.2)	13 (3.8)	0.004
Acute myocardial infarction	16 (1.6)	11 (3.3)	2 (0.6)	3 (0.9)	0.013
FEV1, L	2.81 (0.98)	2.55 (0.91)	2.88 (0.96)	3.02 (0.99)	<0.001
FVC, L	3.65 (1.17)	3.34 (1.07)	3.71 (1.19)	3.90 (1.19)	<0.001
FEV1/FVC	0.77 (0.08)	0.76 (0.09)	0.77 (0.08)	0.77 (0.08)	0.09
Obstructive lung function	167 (16.1)	64 (18.3)	54 (15.8)	49 (14.1)	0.31
Laboratory work					
Total cholesterol, mmol/L	5.58 (1.16)	5.6 (1.2)	5.6 (1.2)	5.5 (1.1)	0.22
Plasma pro-BNP, pmol/L	15 (7–28)	17 (8–30)	15 (8–29)	14 (7–25.5)	0.041
eGFR, mL/min per 1.73 m^2	73 (20)	72 (20)	72 (22)	75 (18)	0.043
Echocardiography					
TAPSE, mm	26 (5)	22 (2)	26 (1)	32 (3)	N/A
LVEF, %	59.8 (1.3)	59.7 (1.5)	59.8 (1.5)	59.9 (0.7)	0.039
LV hypertrophy	248 (23.9)	93 (26.6)	81 (23.7)	74 (21.3)	0.10
LVIDd, cm	4.8 (0.5)	4.6 (0.5)	4.8 (0.5)	4.8 (0.5)	<0.001
LVMI, g/m^2	84.3 (20.7)	85.0 (22.4)	82.7 (18.5)	85.2 (20.8)	0.89
Left atrium dimension, cm	3.4 (0.4)	3.4 (0.4)	3.4 0.4)	3.4 (0.4)	0.10
E/e′	10.7 (4.2)	11.6 (4.7)	10.3 (3.7)	10.1 (4.1)	<0.001
E/A	1.12 (0.43)	1.05 (0.43)	1.15 (0.41)	1.15 (0.44)	0.002
Deceleration time, ms	166 (41)	170 (43)	162 (38)	166 (41)	0.29
s′, cm/s	6.0 (1.2)	5.7 (1.2)	6.0 (1.1)	6.2 (1.3)	<0.001
e′, cm/s	7.4 (2.7)	6.6 (2.5)	7.6 (2.6)	8.0 (2.8)	<0.001
a′, cm/s	6.5 (1.9)	6.6 (2.0)	6.4 (1.8)	6.5 (1.9)	0.28

Data are given as number, number (percentage), or mean (SD). a′ Indicates peak late diastolic velocity; BPM, beats per minute; e′, peak early diastolic velocity; E/A, early/late diastolic inflow velocity; E/e′, ratio of the E wave/e′; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LV, left ventricular; LVEF, LV ejection fraction; LVIDd, LV inner diameter at end diastole; LVMI, LV mass index; N/A, not applicable; pro-BNP, pro-B-type natriuretic peptide; s′, peak systolic tissue velocity; TAPSE, tricuspid annular plane systolic excursion.

Table 3. Univariable and Multivariable Cox Regression to Assess the Prognostic Value of TAPSE in Predicting Cardiovascular Outcomes in the General Population

	CVD (n=69)		NCD (n=162)	
TAPSE, per 1-mm Decrease	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Unadjusted				
	1.13 (1.07–1.20)	<0.001	1.06 (1.03–1.10)	<0.001
Model 1				
	1.08 (1.02–1.14)	0.005	1.04 (1.00–1.07)	0.051
Model 2				
	1.08 (1.01–1.15)	0.017	1.03 (0.98–1.07)	0.19

Model 1 is adjusted for age, sex, systolic blood pressure, hypertension, cholesterol levels, smoking, and diabetes mellitus. Model 2 is adjusted for the same variables as model 1 with the addition of left ventricular mass index, left ventricular internal diameter at end diastole, left ventricular ejection fraction, left atrium dimension, pro-B-type natriuretic peptide, ratio of the E wave/peak early diastolic velocity, and prevalent ischemic heart disease. CVD indicates cardiovascular death; NCD, non-CVD; TAPSE, tricuspid annular plane systolic excursion.

experienced CVD displayed lower values of TAPSE, LVEF, early/late diastolic inflow velocity, s′, and e′ (Table 1). They also displayed higher values of LV mass index, left atrium dimension, E/e′, and deceleration time of the E-wave (Table 1). Finally, participants who experienced CVD had lower rates of FEV1, forced vital capacity, FEV1/forced vital capacity and a higher prevalence of obstructive lung function at baseline (Table 1).

Baseline Characteristics, According to Tertiles of TAPSE

At baseline, decreasing RV systolic function, assessed as TAPSE, was associated with older age, higher systolic blood pressure, higher heart rate, higher pro-B-type natriuretic peptide (pro-BNP), and decreasing values of estimated glomerular filtration rate (Table 2). Decreasing RV systolic function was also associated with increasing prevalence of hypertension, ischemic heart disease, and previous acute myocardial infarction (Table 2). Furthermore, decreasing RV systolic function, as determined by TAPSE, was associated with decreasing values of LVEF, LV inner diameter at end diastole, early/late diastolic inflow velocity, s′, and e′ (Table 2). Decreasing RV systolic function was also associated with increasing values of E/e′ (Table 2). Last, decreasing RV systolic function was associated with decreasing values of FEV1 and forced vital capacity (Table 2).

Association of RV Systolic Function With Other Echocardiographic Parameters

After adjusting for differences in clinical risk factors and comorbidities, decreasing RV function, as determined by TAPSE, was significantly associated with decreasing s′, e′, and left atrium dimension (Table S2).

Prognostic Value of RV Function, Determined by TAPSE, in Predicting CVD

The risk of CVD increased significantly with decreasing RV function, as assessed by TAPSE (Table 3, Figure). Participants in the first (worst) tertile of RV function, as determined by TAPSE, displayed an ≈3.5 times greater risk of CVD when compared with participants in the third (best) tertile (first versus third tertile: hazard ratio [HR], 3.49; 95% CI, 1.87–6.53; *P*<0.001). A nonlinear relationship between decreasing RV systolic function, determined by TAPSE, and the risk of CVD was found (Figure). TAPSE values above ≈24 mm did not appear to be associated with an increased risk of experiencing CVD (Figure). However, the risk of CVD appeared to increase with decreasing values of TAPSE for TAPSE values below ≈24 mm (Figure).

In a multivariable model adjusting for age, sex, systolic blood pressure, hypertension, cholesterol, smoking, and diabetes mellitus, decreasing RV function, as determined by TAPSE, was an independent predictor of CVD (Table 3, model 1). In a final multivariable model adjusting for the same variables as in model 1 with the addition of LV mass index, LV inner diameter at end diastole, LVEF, left atrium dimension, pro-BNP, E/e′, and prevalent ischemic heart disease, RV function by TAPSE remained an independent predictor of CVD (Table 3, model 2). This relationship persisted with additional adjustment for obstructive lung function (HR, 1.08; 95% CI, 1.01–1.14; *P*=0.017 per 1-mm decrease). Similarly, TAPSE remained an independent predictor of outcome when the final multivariable model was additionally adjusted for estimated glomerular filtration rate (HR, 1.08; 95% CI, 1.01–1.15; *P*=0.017 per 1-mm decrease). Even when confining our final multivariable model to participants with normal RV systolic function (TAPSE ≥17 mm), RV function by TAPSE remained an independent predictor of CVD (model 2: HR, 1.07; 95% CI, 1.00–1.15; *P*=0.046 per 1-mm decrease). Similar results were

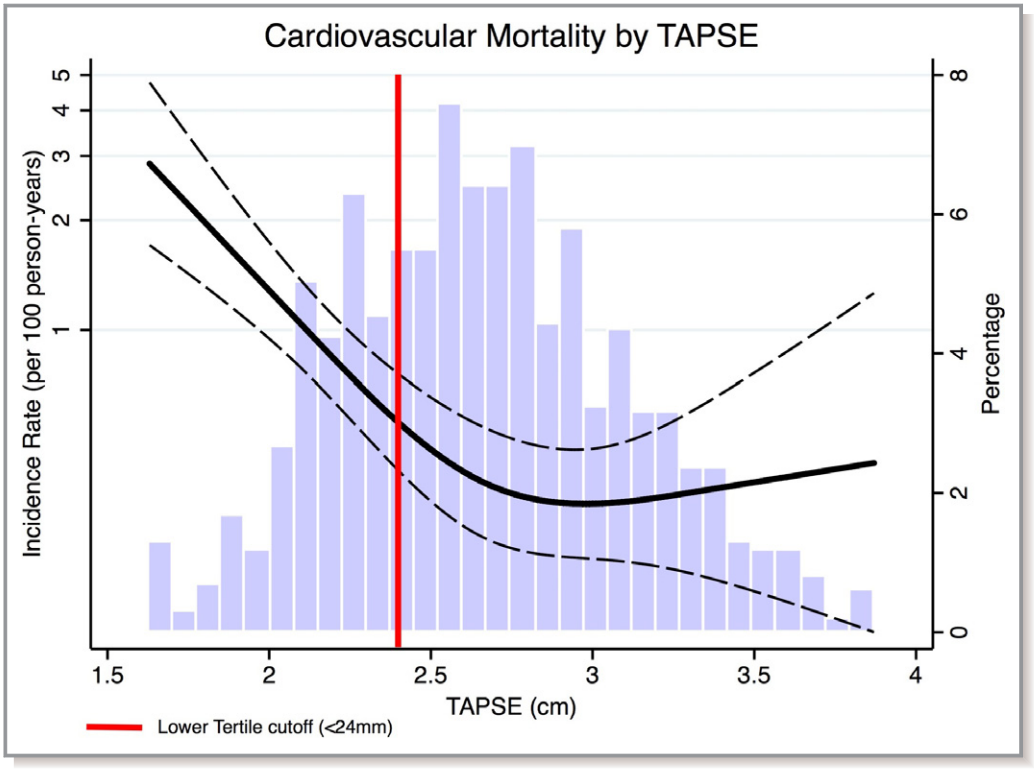

Figure. Tricuspid annular plane systolic excursion (TAPSE) and long-term risk of cardiovascular death in the general population. The figure displays the unadjusted incidence rate of cardiovascular death per 100 person-years as a function of TAPSE. Test for overall relationship, $P<0.001$. Test for nonlinearity, $P=0.008$. Dashed lines represent 95% CIs. The vertical red line represents the cutoff for the lower tertile of TAPSE values.

found when confining our analysis to participants with normal RV systolic function (TAPSE ≥17 mm) and normal LV systolic function (LVEF ≥60%) (model 2: HR, 1.08; 95% CI, 1.01–1.16; $P=0.031$ per 1-mm decrease).

Incremental Prognostic Value of RV Function in Predicting CVD in the General Population

Adding the presence of decreased RV systolic function (defined as the lower tertile of TAPSE values, TAPSE <24 mm) to established cardiovascular risk factors from the SCORE risk chart, a modified version of the AHA/ACC Pooled Cohort Equation, or a modified version of the Framingham Risk Score significantly improved risk classification with respect to CVD (Table S3). In contrast, LVEF, E/e′, and pro-BNP did not significantly improve risk classification of individuals from the general population with respect to CVD (Table S3).

Discussion

In this study, we found RV systolic function, as assessed by TAPSE, to be an independent predictor of CVD in the general population. Furthermore, assessing RV systolic function added incremental prognostic value in predicting CVD in the general population in addition to established cardiovascular risk factors from the SCORE risk chart and a modified version of the AHA/ACC Pooled Cohort Equation. In contrast, LVEF, E/e′, and pro-BNP levels did not contribute with incremental prognostic information. To our knowledge, this is the largest study to date assessing the prognostic value of RV systolic function in predicting cardiovascular outcomes in the general population with long-term follow-up.

TAPSE and RV Systolic Function

Assessment of the RV systolic function may be beneficial for risk stratification of individuals from the general population. This may be because of TAPSE's simplicity, ease of measurement, and good reproducibility.[19] It does not require state-of-the art image quality or high-frame rate conditions for optimal measurement,[19] as is the case for other measures of RV systolic function, such as 2-dimensional speckle tracking of the RV free wall.[19] In addition, it can often be hard to acquire high-quality images of the entire RV free wall, whereas imaging only the RV base and tricuspid annular plane is much more feasible. Despite its simplicity, TAPSE correlates well

with RV ejection fraction determined by radionucleotide angiography.[19,20]

Normal RV Systolic Function in the General Population

Current guidelines define the normal range of RV systolic function determined by TAPSE in the general population as a mean±SD of 24±3.5 mm.[14] In our sample from the general population, values of TAPSE were higher (mean, 26 mm; SD, 5 mm). The reason for the higher values of TAPSE seen in this study is unclear. In current guidelines, abnormal RV systolic function is defined as TAPSE <17 mm.[14] In our study, a TAPSE of ≤17 mm was significantly associated with a higher risk of CVD, as shown by the Figure. However, the Figure also revealed that the risk of CVD increases with decreasing values of TAPSE already once TAPSE is below ≈24 mm, which is currently considered within the normal range.[14] Furthermore, we show that participants in the lower tertile of RV systolic function, as determined by TAPSE (TAPSE <24 mm), are at an increased risk of experiencing CVD. Also, in our final multivariable model adjusting for clinical and echocardiographic parameters, RV systolic function by TAPSE remained an independent predictor of CVD, even when confining our analysis to participants with a normal TAPSE (TAPSE ≥17 mm) and a normal LV systolic function (LVEF ≥60%). These findings suggest that defining abnormal RV systolic function as TAPSE <17 mm may be conservative. However, more research is needed to validate our findings.

Prognostic Value of RV Systolic Function in the General Population

At the current moment, little evidence exists on the prognostic value of RV systolic function in the general population. Kawut et al evaluated RV systolic function in the MESA (Multi-Ethnic Study of Atherosclerosis), assessed as RV ejection fraction by cardiac magnetic resonance imaging, and found that RV systolic function was not significantly associated with a composite outcome of HF and CVD.[21] However, differences in study populations and follow-up duration make direct comparisons with our study difficult. Kawut et al[21] studied a sample composed of ≈40% whites, 30% blacks, 20% Hispanics, and 10% Chinese, whereas our study sample was composed almost entirely of whites. In addition, in their study, all participants with cardiovascular disease were excluded, whereas we only excluded participants with HF; and the prevalence of cigarette smoking at baseline was much lower in their study compared with ours (12% versus 35%). Thus, when compared with our study sample, Kawut et al[21] studied an ethnically diverse, healthier population, and this may partly explain the differences between our results. In addition, our follow-up duration was over twice the follow-up duration in the study by Kawut et al[21] (mean, 5.8 years, versus median, 12.7 years). This could also contribute to the difference between our results because it is possible that RV systolic function may be particularly associated with long-term outcome in the general population.

In our study, RV function, determined by TAPSE, was superior to E/e′, pro-BNP, and LVEF in predicting CVD in the general population. Decreased RV systolic function is often a marker of advanced and progressed disease in HF. In the absence of cardiovascular disease, with normal pulmonary vasculature, the LV is capable of sustaining the circulatory needs of the body, even without RV function.[22] As the LV diastolic or systolic function becomes impaired, increasing levels of RV compensation are needed to sustain cardiac output and minimize venous congestion.[23] Thus, right-sided heart function is adversely affected by deteriorating LV function through circulatory coupling. Accordingly, it is known that LV diastolic dysfunction may cause pulmonary hypertension.[11,24] RV systolic function, assessed by TAPSE, is decreased in pulmonary hypertension and is a powerful predictor of outcome.[25] Hence, it is possible that RV systolic function, assessed as TAPSE, is an integrated marker of LV diastolic dysfunction, a condition that is relatively common in the aging general population[26] and is associated with cardiovascular morbidity and mortality.[12] This is supported by our results because TAPSE was significantly associated with e′ and left atrial size, both of which reflect diastolic function. Also, LV systolic function is a significant determinant of RV systolic function through mechanical interventricular dependence.[27] In our study, decreasing RV systolic function, as determined by TAPSE, was significantly associated with decreasing systolic LV function, as determined by s′ after adjustment for differences in clinical risk factors. Because s′ has been previously shown to predict CVD in the general population,[28] some of the prognostic value of RV function with respect to CVD may also be because of its relation to LV systolic performance through interventricular dependence. However, although we adjusted for systolic function as determined by LVEF, RV function, determined by TAPSE, remained a strong predictor of CVD.

HF is a significant contributor to CVD.[29] Interestingly, RV systolic dysfunction has been found to be more frequent in idiopathic dilated cardiomyopathy when compared with ischemic cardiomyopathy.[30] This indicates that RV systolic dysfunction may be associated with generalized myocardial disease, independent of ischemic disease. Thus, some of the prognostic value of RV function, determined by TAPSE, in predicting CVD in the general population may be because of its ability to detect early cardiomyopathy independent of LV dysfunction attributable to ischemic and hypertensive heart disease. This may also explain part of why RV systolic function

remained an independent predictor of CVD, even after adjusting for diastolic function (as determined by E/e′, pro-BNP, and left atrial size) in our final multivariable model.

Future Perspectives and Limitations

Little evidence about the prognostic value of RV systolic function in predicting CVD in the general population with long-term follow-up exists. Our results should be considered exploratory and hypothesis generating. Strengths of the present study are a large sample of individuals from the general population and long-term complete follow-up. A limitation of the present study is the lack of information on RV systolic pressure. It would be interesting to assess whether the prognostic value of RV systolic function is independent of RV afterload. Unfortunately, information on RV systolic pressure was not available in this study. Another limitation is the large number of patients who had to be excluded because of inadequate image quality for measuring TAPSE, although measurement of TAPSE is highly feasible in most patients.[19] Because the echocardiograms were obtained in 2001 to 2003 using less sophisticated hardware than what is available today, and because the original image protocol was not specifically designed to assess RV function, the number of patients who had to be excluded was significantly higher than what would be expected using contemporary equipment and a protocol designed to optimize RV imaging. Because excluded participants were significantly older, had a higher blood pressure, and had a higher body mass index, this may potentially have introduced a selection bias. However, although many high-risk patients were excluded because of inadequate images for the measurement of TAPSE, we still found significant associations between TAPSE and CVD, despite rigorous adjustment for clinical, echocardiographic, and lung function parameters. Nonetheless, if a selection bias was introduced, this could affect the generalizability of our results and, therefore, our results should be confirmed in future studies.

Conclusion

RV systolic function, as assessed by TAPSE, is associated with CVD in the general population. In the general population, assessment of RV systolic function may provide novel prognostic information about the risk of CVD.

Disclosures

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Supplemental Material

Table S1. Comparison of participants included in the study with participants excluded due to either heart failure, atrial fibrillation or suboptimal image quality for measurement of tricuspid annular plane systolic excursion.

Demographics	Study sample	Excluded participants	P-value
N	1039	1182	
Age (years)	57.2 (16.1)	60.3 (15.9)	<0.001
Male	398 (39.6%)	535 (45.0%)	0.010
Clinical Characteristics			
Systolic blood pressure (mmHG)	133.5 (23.0)	138.1 (22.2)	<0.001
Diastolic blood pressure (mmHG)	77.6 (12.3)	78.8 (12.0)	0.023
Pulse Pressure (mmHG)	55.9 (18.2)	59.3 (18.2)	<0.001
Mean arterial pressure (mmHG)	96.1 (14.2)	98.4 (13.7)	<0.001
Hypertension	392 (39.0%)	579 (49.1%)	<0.001
Smoking	352 (35.6%)	314 (31.7%)	0.07
Body mass index (kg/m^2)	25.3 (3.8)	25.8 (4.1)	0.008
Diabetes Mellitus	96 (9.6%)	141 (11.9%)	0.08
Heart rate (BPM)	66.5 (11.2)	68.1 (11.8)	0.001

Table S2. Multivariable linear regression analysis to determine associations between TAPSE and other echocardiographic parameters in the general population.

	Univariable		Multivariable*	
Parameter	**Standardized ß-coefficient (std error)**	**P-Value**	**Standardized ß-coefficient (std error)**	**P-Value**
LVEF (%)	0.06 (0.01)	0.044	0.05 (0.01)	0.10
Hypertrophy	-0.05 (0.03)	0.08	-0.01 (0.4)	0.79
LVIDd/BSA (cm)	0.01 (0.06)	0.71	0.02 (0.06)	0.57
LVMI (g/m^2)	0.02 (0.14)	0.59	0.07 (0.01)	0.09
LAd (cm)	0.07 (0.04)	0.025	0.11 (0.04)	0.002
E/e'	-0.13 (0.36)	<0.001	-0.06 (0.45)	0.15
E/A	0.11 (0.03)	0.001	0.01 (0.05)	0.76
DT (ms)	-0.03 (0.37)	0.30	0.03 (0.40)	0.43
s' (cm/s)	0.15 (0.01)	<0.001	0.11 (0.01)	0.005
e' (cm/s)	0.21 (0.01)	<0.001	0.26 (0.01)	<0.001
a' (cm/s)	-0.03 (0.01)	0.33	0.05 (0.01)	0.22

*The multivariable model is adjusted for age, sex, cholesterol, smoking, systolic blood pressure, hypertension, diabetes, prevalent ischemic heart disease.

TAPSE, tricuspid annular plane systolic excursion; LVEF, left ventricular ejection fraction; LVIDd, left ventricular inner diameter at end diastole; LVMI ,left ventricular mass index; LAd, left atrium dimension; DT, deceleration time.

Table S3. Net Reclassification Improvement analysis.

SCORE risk chart	Net Reclassification Improvement
Decreased RV systolic function (TAPSE<24mm)	Continuous NRI 0.522, 95% CI 0.072-0.765*
LVEF	Continuous NRI 0.185, 95% CI -0.353-0.528
E/e'	Continuous NRI -0.078, 95% CI -0.385-0.495
pro-BNP	Continuous NRI -0.186, 95% CI -0.542-0.239
Modified ACC/AHA Pooled Cohort Equation	Net Reclassification Improvement
Decreased RV systolic function (TAPSE<24mm)	Continuous NRI 0.509, 95% CI 0.026-0.757*
LVEF	Continuous NRI 0.236, 95% CI -0.369-0.528
E/e'	Continuous NRI -0.160, 95% CI -0.416-0.503
pro-BNP	Continuous NRI -0.129, 95% CI -0.498-0.212
Framingham risk score	Net Reclassification Improvement
Decreased RV systolic function (TAPSE<24mm)	Continuous NRI 0.496, 95% CI 0.016-0.757*
LVEF	Continuous NRI 0.265, 95% CI -0.335-0.573
E/e'	Continuous NRI -0.185, 95% CI -0.451-0.510
pro-BNP	Continuous NRI -0.235, 95% CI -0.519-0.228

Net Reclassification Improvement analysis to evaluate incremental prognostic value of adding the presence of decreased RV systolic function to established cardiovascular risk factors. Decreased RV systolic function is defined as a TAPSE of less than the cutoff-value for the lower tertile of TAPSE values (TAPSE<24mm). SCORE risk chart cardiovascular risk factors are age, sex, cholesterol levels, systolic blood pressure and smoking status. The modified ACC/AHA Pooled Cohort Equation risk factors are age, sex, cholesterol levels, systolic blood pressure, smoking status, hypertension status and diabetes status (race was not included, since the inhabitants of Denmark are mainly white). Framingham risk score risk factors are age, systolic blood pressure, total cholesterol, blood pressure medication, smoking and diabetes (HDL cholesterol was not included since this information was not available). RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; LVEF, left ventricular ejection fraction.