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Associations between cardiovascular risk factors, biomarkers, and left ventricular mechanical dispersion: insights from the ACE 1950 Study

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Aims Mechanical dispersion measures left ventricular contraction heterogeneity and is associated with the risk of sudden cardiac death. However, the associations between mechanical dispersion and cardiovascular risk factors in early mid-life, and established biomarkers of sub-clinical myocardial injury and dysfunction are not known. We aimed to examine this in the general population.

Methods and results During 2012–15, we included 2527 Norwegian individuals from the general population born in 1950, with measurements of mechanical dispersion by 2D speckle tracking echocardiography and concentrations of high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) available. Mechanical dispersion was calculated as the standard deviation of the contraction duration of 17 strain segments. We assessed the associations between mechanical dispersion, concentrations of hs-cTnT and NT-proBNP, and cardiovascular risk factors collected at a national health screening survey two decades earlier. At echocardiography baseline, median age was 64 (interquartile range 63.5–64.5) years, 49.8% were women, 59.1% had hypertension, and 5.9% reported established coronary artery disease. Median mechanical dispersion was 38.0 (29.5–47.0) ms, median hs-cTnT concentration 6 (4–8) ng/L, and the median NT-proBNP concentration 54 (34–93) ng/L. Mechanical dispersion was associated with both hs-cTnT and NT-proBNP concentrations in multivariable models adjusted for clinical and echocardiographic variables. High body mass index, serum triglyceride concentrations, and low resting heart rate at Age 40 were independently associated with increased mechanical dispersion two decades later.

Conclusion Established risk factors at Age 40 are associated with mechanical dispersion two decades later, and mechanical dispersion is cross-sectionally associated with biomarkers of subclinical myocardial injury and dysfunction.

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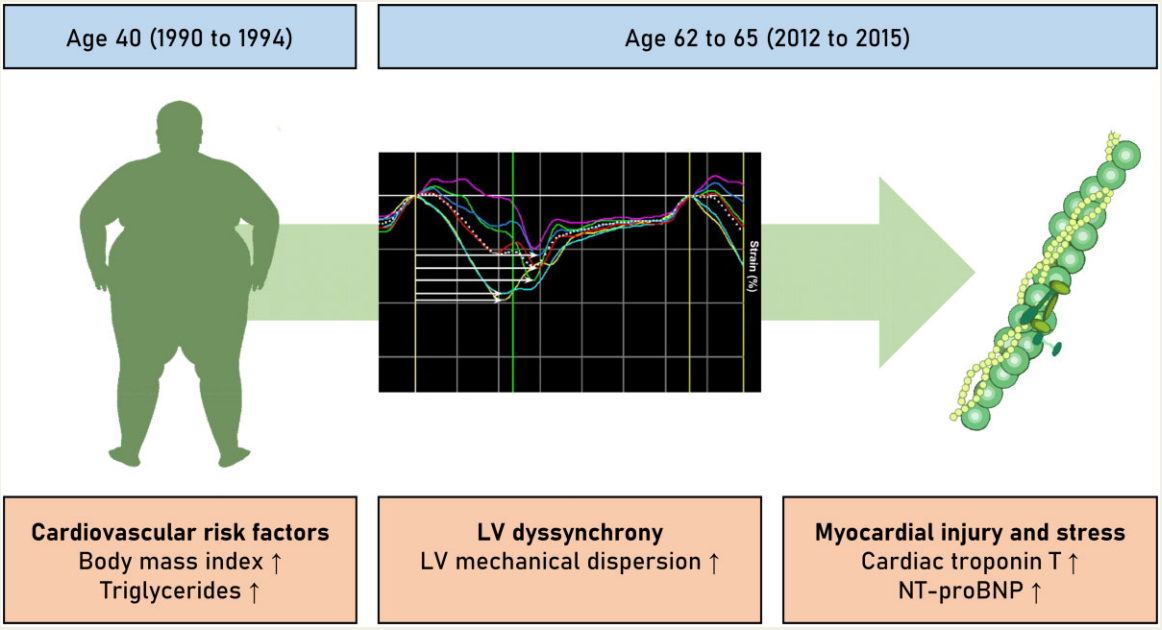
Graphical Abstract



Keywords Mechanical dispersion • Two-dimensional speckle tracking echocardiography • Myocardial strain • Cardiac biomarkers • General population

Introduction

Heart failure is one of the most common causes of morbidity and mortality in the Western world.[1] Circulating biomarkers identify subjects at increased risk of heart failure[2] but are less accurate to identify specific pathophysiologic mechanisms like the risk of future ventricular arrhythmias.[3] Recently, novel imaging-based risk markers by echocardiography like mechanical dispersion have been identified, which seem to predict incident ventricular arrhythmias and death in patients with established cardiovascular (CV) disease.[4]

Mechanical dispersion measures the heterogeneity of the contraction pattern of the left ventricle (LV) and is derived from global longitudinal strain (GLS) by two-dimensional speckle tracking echocardiography (2D STE). A higher value of mechanical dispersion reflects a more dyssynchronous LV contraction pattern, which may increase the risk of ventricular arrhythmias.[4] We have previously shown that in the general population, coronary artery disease (CAD) and hypertension are associated with higher mechanical dispersion.[5] Additionally, a recent publication reports that mechanical dispersion in the general population was associated with cardiac death.[6] CV risk factors during early adulthood may impact the progression of mechanical dispersion, but currently, no information is available regarding the association between clinical risk factors in the early forties and mechanical dispersion at age ~65 years.

Mechanical dispersion has also been proposed to reflect fibrosis and electromechanical changes in the myocardium, but whether this transcends to middle-aged subjects from the general population is not known.[7,8] Cardiac biomarkers like high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are considered surrogate markers for subclinical myocardial injury and dysfunction.[9–13] We propose that mechanical dispersion is associated with cardiac biomarkers of subclinical myocardial injury and dysfunction.[14–16] Using a cohort of late mid-life individuals recruited from the general population, the current study aimed to test the hypotheses that (1) clinical CV risk factors in the early forties are associated with mechanical dispersion two decades later, and (2) mechanical dispersion measured in mid-sixties correlates cross-sectionally with cardiac biomarkers of subclinical myocardial injury and dysfunction.

Methods

Study population

The study design and methods of the Akershus Cardiac Examination (ACE) 1950 Study have been described previously.[17] In short, all residents of Akershus County, Norway, born in 1950 were invited to participate in a prospective population-based health examination study. In total, 3706 individuals participated (participation rate 63.6%), and were extensively evaluated regarding CV risk factors and disease with a baseline study visit performed for all participants. The study participants were aged 63–65 years at study inclusion, which was performed between 2012 and 2015 at two study sites (Akershus University Hospital and Bærum

Hospital). In the present study, we included participants with echocardiographic recordings avaiable for mechanical dispersion analyses by 2D STE ($n = 2529$) that also had available measurements of the biomarkers hs-cTnT and NT-proBNP ($n = 2527$). Previously, 1906 (75.4%) of the participants from the present study had also attended another Norwegian nationwide health survey that included self-assessed questionnaires, clinical examination, and non-fasting blood sampling (The Age 40 Program, *Figure 1*). The survey was conducted by the National Health Screening Service and aimed to investigate the CV risk profile of 40-year-olds. This national survey was performed between 1990 and 1994 for participants born in 1950, approximately two decades before the baseline visit of the ACE 1950 Study. Accordingly, we have measured and self-reported data on CV risk factors in the early forties from the majority of our participants, and prior to the potential development of CV disease. One participant with a self-reported history of premature myocardial infarction at the Age 40 Program was excluded from the analysis.

The ACE 1950 Study participants provided written informed consent before study inclusion and the consent also permitted linkage of data from previous Norwegian health studies. The study complies with the Declaration of Helsinki and was approved by the Regional Ethics Committee with reference number 2011/1475, and is registered at Clinicaltrials.Gov with registration number NCT01555411.

Echocardiography at the ACE 1950 Study baseline visit

We performed transthoracic echocardiography using Vivid E9 (GE Healthcare, Horten, Norway) and images were stored digitally and later analysed off-line using EchoPac version 201 (GE Healthcare, Horten, Norway). The methods for echocardiography recordings and analyses were performed according to a predefined study protocol and have previously been described in detail.[5] LV systolic function was assessed by LV ejection fraction (EF) according to the modified Simpson's biplane method, and GLS and mechanical dispersion were determined by 2D STE. GLS was analysed semi-automatically by tracing the mid-wall myocardium in three apical views, averaging peak systolic strain values from 17 strain segments.[18,19] Two cardiac cycles were measured. The region of interest was adjusted to fit the myocardial thickness, and the operator manually adjusted segments that failed to track. Segments that subsequently failed to track properly were excluded, and the whole analysis was excluded if more than one segment per image view, or more than two segments in total failed to track properly. Peak systolic strain was defined as maximal peak negative strain during systole, where the start of systole was defined by R wave on the electrocardiogram (ECG) and end of systole defined by the aortic valve closure in apical long-axis view. Mechanical dispersion was calculated automatically by EchoPac as the standard deviation (SD) of contraction duration of 17 strain segments. Contraction duration was defined as the time from R wave on ECG to peak negative strain, regardless of the aortic valve closure (*Figure 2*).

LV mass was calculated from M-mode measurements according to the method described by Devereux *et al.*[20] Diastolic function was assessed by the average of septal and lateral peak early diastolic velocity by tissue velocity imaging (e'), the ratio between peak early diastolic velocity (E) by pulsed Doppler and e' (E/e'), maximal tricuspid regurgitation velocity (TR V_{max}) and left atrial (LA) volume index (end-systolic volume/body surface area). Indexed measures were calculated using body surface area by the Mosteller formula.[21] Cardiac dimensions and established indices of systolic and diastolic function were analysed according to current guidelines.[19,22]

Intra-observer and inter-observer variability testing were performed by two observers (E.N.A. and B.K.) in 15 randomly selected patients for GLS and mechanical dispersion, and expressed by intra-class correlation values.

Circulating biomarkers and blood sampling at the ACE 1950 Study baseline visit

Fasting peripheral venous blood samples were drawn on the same day as the echocardiographic recordings in the ACE 1950 Study, centrifuged at

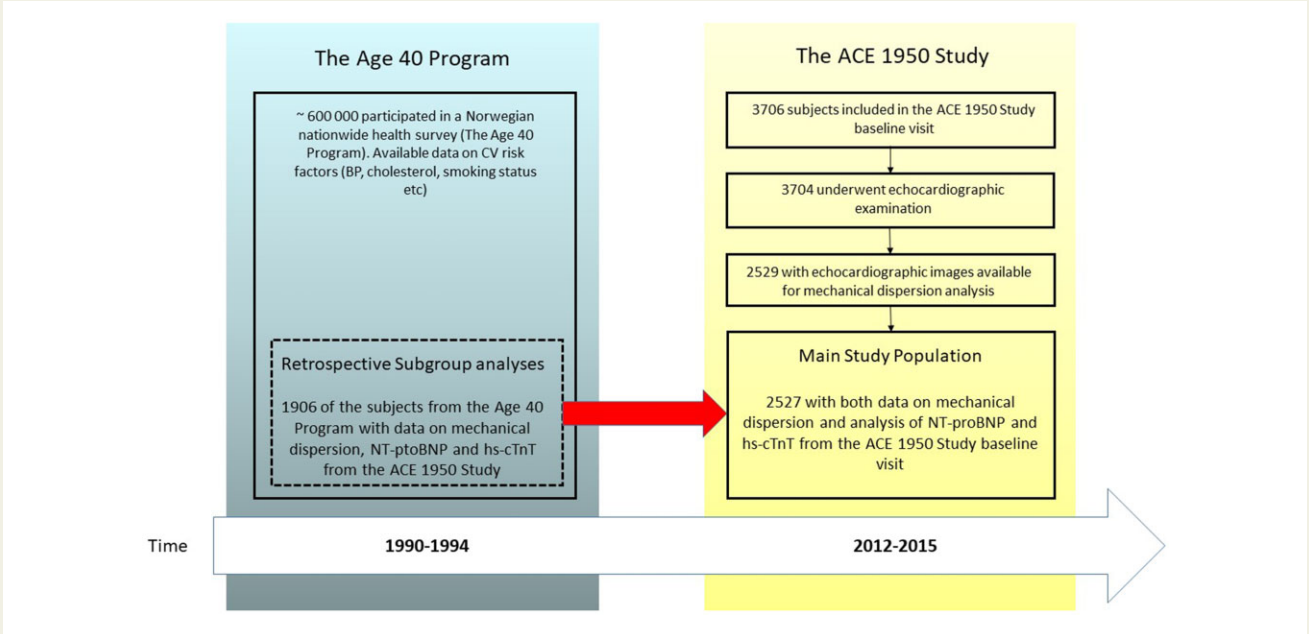


Figure 1 Overview of the study population, including timeline. The ACE 1950 Study was performed when the participants were 64 years old, and the Age 40 Program when the participants were 40 years old.

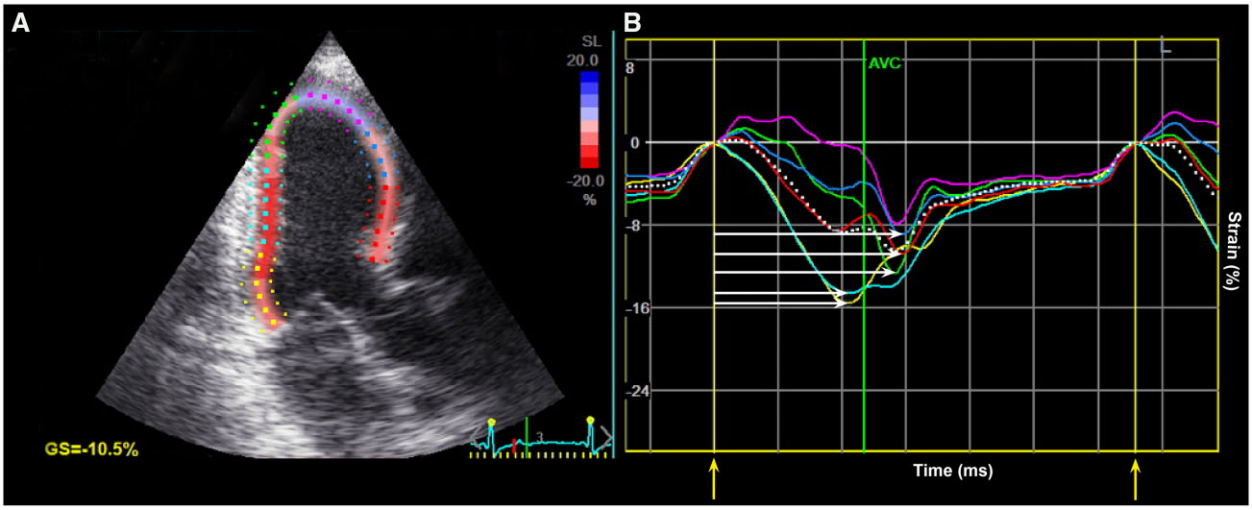


Figure 2 (*A*) Strain tracing of apical long-axis view. (*B*) Strain curves from same image. Yellow vertical arrows indicate R on the electrocardiogram. White horizontal arrows demonstrate contraction duration per strain segment. Mechanical dispersion was defined as standard deviation of contraction duration of all segments. AVC, aortic valve closure.

room temperature and serum was frozen at -80°C. NT-proBNP and hs-cTnT concentrations are considered stable when stored at -80°C.[23,24] Both biomarkers were analysed between October 2017 and January 2018 at Akershus University Hospital, Norway. NT-proBNP and hs-cTnT concentrations were measured on Cobas Platform 8000, e801 (Roche Diagnostics, Rotkreuz, Switzerland) using the proBNP II assay and the STAT hs-Troponin T assay. For NT-proBNP, the limit of detection (LoD) was 5.0 ng/L and the limit of blank (LoB) was 3.0 ng/L, and for hs-cTnT LoD was 3.0 ng/L and LoB was 2.5 ng/L. Study participants with concentrations below the LoD were given a concentration of 2.5 ng/L for NT-proBNP and 1.5 ng/L for hs-cTnT.

Details regarding serum cholesterol variables and renal function are found in Supplementary material online, *Methods*.

Clinical variables at the ACE 1950 Study and Age 40 Program study visits

Demographic and clinical variables from the ACE 1950 Study participants have been previously reported.[5] Details concerning variables from the ACE 1950 Study baseline visit and the Age 40 Program are presented in the Supplementary material online, *Methods*.

Statistical analysis

Baseline characteristics were reported according to the median value of mechanical dispersion (38 ms) in our cohort. Continuous variables were reported as median (interquartile range), and categorical variables as absolute numbers (percentages). Comparisons of groups were made by the Mann–Whitney *U* test for continuous variables and by χ^2 tests for categorical variables. Comparisons of paired samples were made by the Wilcoxon Signed Rank test for continuous variables and by the McNemar's Test for categorical variables. Due to a highly right-skewed distribution, hs-cTnT and NT-proBNP concentrations were transformed by the natural logarithm prior to regression analyses. hs-TnT and NT-proBNP concentrations were used as dependent variables to assess the associations with mechanical dispersion, GLS and LVEF in multivariable linear regression analyses. We assessed the associations of mechanical dispersion, GLS, and LVEF with hs-cTnT and NT-proBNP separately for each echocardiographic index and in analyses in which all three indices were included. We adjusted for the study sites at the ACE 1950 Study baseline visit, demographic data and *a priori* selected variables associated with CV risk. We also adjusted for current statin therapy, as it may attenuate associations with cardiac troponins.[25] We performed the regression analysis in the following fashion: Model 1, unadjusted; Model 2, adjusted for age and sex; and Model 3, adjusted for age, sex, study site, higher education level, body mass index (BMI), estimated glomerular filtration rate (eGFR), total cholesterol, high-density lipoprotein (HDL) cholesterol, diabetes mellitus, hypertension, CAD, statin therapy, and current smoking.

We performed linear regression analyses using data from the Age 40 Program to determine whether CV risk factors in the early forties were associated with increased mechanical dispersion in the mid-sixties. Mechanical dispersion obtained at the ACE 1950 Study baseline visit was used as a dependent variable, and we performed univariate and multivariable linear regression analysis with *a priori* selected variables obtained at the Age 40 Program visit: Age at the Age 40 Program visit, sex, resting heart rate, systolic and diastolic blood pressure, BMI, inactive lifestyle, hypertensive medication, diabetes mellitus, current smoking, and non-fasting serum total cholesterol and triglyceride concentrations. We performed three sensitivity analyses on the associations between CV risk factors and mechanical dispersion: (1) Entering only variables with a *P*-value <0.05 in univariate analysis in to the final multivariable analysis, (2) additionally adjusting the multivariable model for established CAD at the ACE 1950 Study baseline visit and (3) additionally adjusting the multivariable model for length of follow-up time between the Age 40 Program and the ACE 1950 Study baseline.

Statistical significance was defined as $P < 0.05$, and we used IBM SPSS Statistics for Windows, version 25.0 and STATA 16 (StataCorp LP, College Station, TX, USA) for the analyses.

RESULTS

Baseline characteristics in the ACE 1950 Study stratified according to median value of mechanical dispersion

Of 2527 participants included in the present study, median age was 64 [interquartile range (IQR) 63.5–64.5] years, 49.8% were women, 59.1% had hypertension, and 5.9% reported established CAD. The median (IQR) value for mechanical dispersion was 38.0 (39.5–47.0) ms and participants with supra-median mechanical dispersion were more often non-Caucasians, obese, and fewer had higher-education (*Table 1*). Participants with high mechanical dispersion values also had a higher prevalence of diabetes mellitus, hypertension, and CAD. The prevalence of current smoking at the ACE 1950 Study baseline visit did not differ between the groups.

Mechanical dispersion and conventional echocardiographic indices in the ACE 1950 Study

Median (IQR) values for LVEF were 56 (52–59)% and median GLS value was -20.2 (-21.8 to -18.5)% in the current study cohort. We found significant differences for echocardiographic indices of systolic function according to mechanical dispersion: LVEF 55 (52–59)% for participants with high mechanical dispersion vs. 56 (53–59)% for participants with low mechanical dispersion ($P = 0.002$) and GLS -19.7 (-21.4 to -17.8)% for participants with high mechanical dispersion vs. -20.6 (-22.2 to -19.2)% for participants with low mechanical dispersion ($P < 0.001$, *Table 2*). The diastolic parameters E/e', e', and LV mass index were also significantly different between participants with high and low mechanical dispersion. The correlation coefficient between mechanical dispersion and LVEF was -0.07 ($P < 0.001$), and the correlation coefficient between mechanical dispersion and GLS was 0.27 ($P < 0.001$). Mechanical dispersion was also significantly correlated with E/e', while GLS and LVEF did not correlate with E/e'. Numerically, correlation coefficients were higher for mechanical dispersion and LV mass index, E/e' and e' compared to the corresponding correlation coefficients for GLS and LVEF (Supplementary material online, *Table S1*). Variability analysis is reported in Supplementary material online, *Results*.

Associations between clinical risk factors in early mid-life and mechanical dispersion two decades later

The median age at participation in the Age 40 Cardiovascular Screening Survey was 40.0 (40.0–40.0) years and of the participants

Table 1 Characteristics at the ACE 1950 Study baseline visit according to median value of mechanical dispersion

	Better	Worse	
Mechanical dispersion	<38.0	≥38.0	*P*-value*
n	1253	1274	
Age (years)	63.9 (63.4–64.4)	64.0 (63.5–64.5)	<0.001
Female sex, n (%)	638 (50.9%)	620 (48.7%)	0.26
Caucasian ethnicity, n (%)	1234 (98.5%)	1240 (97.3%)	0.043
Higher education, n (%)	621 (49.7%)	554 (43.7%)	0.002
Body mass index (kg/m^2)	25.6 (23.4–28.1)	26.6 (24.5–29.1)	<0.001
Systolic blood pressure (mmHg)	134 (122–146)	139 (127–152)	<0.001
Diastolic blood pressure (mmHg)	76 (69–82)	77 (71–84)	<0.001
Heart rate (beats/min)	61 (55–68)	61 (55–67)	0.43
Current smoker, n (%)	187 (15.0%)	164 (12.9%)	0.14
COPD, n (%)	101 (8.1%)	83 (6.6%)	0.13
Obesity, n (%)	164 (13.1%)	235 (18.4%)	<0.001
Diabetes mellitus, n (%)	67 (5.4%)	103 (8.1%)	0.006
Hypertension, n (%)	648 (51.7%)	845 (66.3%)	<0.001
Coronary artery disease, n (%)	43 (3.4%)	105 (8.2%)	<0.001
Total cholesterol (mmol/L)	5.4 (4.8–6.1)	5.5 (4.7–6.2)	0.91
HDL cholesterol (mmol/L)	1.6 (1.3–1.9)	1.5 (1.2–1.8)	<0.001
eGFR (mL/min/1.73 m^2)	85.4 (75.5–92.5)	84.0 (74.7–92.2)	0.11
hs-cTnT (ng/L)	6.0 (4.0–8.0)	6.0 (4.0–9.0)	0.001
NT-proBNP (ng/L)	54.0 (33.8–90.0)	56.0 (33.8–93.0)	0.21
Beta blocker, n (%)	109 (8.7%)	172 (13.5%)	<0.001
ACEi or ARB, n (%)	243 (19.4%)	370 (29.0%)	<0.001
Statins, n (%)	279 (22.3%)	340 (26.7%)	0.011

Values are median (IQR) or *n* (%).
*Comparisons according to median value of mechanical dispersion.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2 Electrocardiographic and echocardiographic characteristics at the ACE 1950 Study baseline visit according to median value of mechanical dispersion

	Better	Worse	
Mechanical dispersion	<38.0	≥38.0	*P*-value*
n	1253	1274	
Atrial fibrillation, n (%)	36 (2.9%)	37 (2.9%)	0.96
Left bundle branch block, n (%)	1 (0.1%)	14 (1.1%)	0.001
Right bundle branch block, n (%)	10 (0.8%)	35 (2.7%)	<0.001
QRS duration (ms)	90 (84–98)	94 (86–100)	<0.001
QTc (ms)	419 (405–434)	424 (409–438)	<0.001
LV EF (%)	56 (53–59)	55 (52–59)	0.002
LV GLS (%)	-20.6 (-22.2–[-19.2])	-19.7 (-21.4–[-17.8])	<0.001
LV mass index	71.0 (62.4–82.4)	76.1 (65.7–89.5)	<0.001
LA volume index	26.1 (22.2–30.9)	26.0 (22.0–31.1)	0.82
e′ average (cm/s)	8.0 (7.0–9.0)	7.2 (6.2–8.2)	<0.001
E/e′	8.2 (6.9–9.6)	8.8 (7.5–10.4)	<0.001
TR V_{max} (m/s)	2.2 (2.1–2.4)	2.2 (2.1–2.4)	0.57

Values are median (IQR) or *n* (%).
*Comparisons according to median value of mechanical dispersion.
e′, peak early diastolic velocity by tissue velocity imaging; *E*, peak early diastolic velocity by pulsed Doppler; EF, ejection fraction; GLS, global longitudinal strain; LA, left atrial; LV, left ventricular; QTc, rate corrected QT-interval. TR V_{max}, maximal tricuspid regurgitation velocity.

51.2% were women. Supplementary material online, *Table S2* reports baseline characteristics of our ACE 1950 cohort from the Age 40 Screening visit ($n = 1906$) and Supplementary material online, *Table S3* presents a comparison between baseline characteristics at the two study visits performed in 1990–94 and 2012–15. High BMI, serum triglyceride concentration, and low resting heart rate in early adult life were independently associated with increasing mechanical dispersion at the ACE 1950 Study baseline visit age 63–65 years (*Table 3*). A sensitivity analysis where only variables with $P < 0.05$ in the univariate regression analysis were included in a multivariable linear regression analysis did not change the results substantially: BMI and triglyceride concentrations remained independently associated with mechanical dispersion, while heart rate was not included in the final model (Supplementary material online, *Table S4*). Adjusting for CAD in the ACE 1950 Study and for follow-up time between the Age 40 Program and the ACE 1950 Study baseline did not alter the results (Supplementary material online, *Table S5* and *S6*).

Table 3 Associations between variables from the Age 40 Program and left ventricular mechanical dispersion

Independent variables from the Age 40 Study	Univariate linear regression		Multivariable linear regression	
	B (95% CI)	*P*-value	B (95% CI)	*P*-value
Age (years)	-1.88 (-3.85 to 0.09)	0.06	-0.80 (-3.07 to 1.48)	0.49
Female sex	-1.72 (-3.04 to -0.41)	0.010	1.02 (-0.57 to 2.61)	0.21
Heart rate (beats/min)	-0.03 (-0.08 to 0.02)	0.26	-0.07 (-0.13 to -0.01)	0.015
Systolic blood pressure (mmHg)	0.10 (0.05 to 0.15)	<0.001	0.03 (-0.05 to 0.10)	0.52
Diastolic blood pressure (mmHg)	0.15 (0.08 to 0.22)	<0.001	0.11 (0.00 to 0.22)	0.05
Treatment for hypertension	3.79 (-2.53 to 10.11)	0.24	1.75 (-4.55 to 8.05)	0.59
Body mass index (kg/m^2)	0.60 (0.38 to 0.82)	<0.001	0.35 (0.11 to 0.59)	0.005
Inactive lifestyle	0.56 (-1.15 to 2.27)	0.52	0.24 (-1.51 to 2.00)	0.79
Diabetes mellitus	-13.13 (-33.51 to 7.25)	0.21	-10.36 (-30.49 to 9.77)	0.31
Current smoking	-0.55 (-1.95 to 0.84)	0.44	-0.38 (-1.84 to 1.08)	0.61
Total cholesterol (mmol/L)	1.51 (0.84 to 2.17)	<0.001	0.73 (-0.03 to 1.48)	0.06
Triglycerides (mmol/L)	1.52 (0.96 to 2.08)	<0.001	0.91 (0.24 to 1.57)	0.007

B, unstandardized coefficient; CI, confidence interval.
In the multivariable linear regression analysis, all variables from univariate linear regression were included.

Cross-sectional associations between mechanical dispersion and hs-cTnT and NT-proBNP concentrations

Median (IQR) hs-cTnT and NT-proBNP concentrations in this sub-study were 6.0 (4.0–8.0) ng/L and 54.0 (33.8–93.0) ng/L. hs-cTnT concentrations were higher in participants with high mechanical dispersion, while NT-proBNP concentrations did not differ significantly between the groups (*Table 1*). No correlation was found between mechanical dispersion and NT-proBNP, while only a weak correlation was found between mechanical dispersion and hs-cTnT (rho = 0.084, $P < 0.001$). When analysed in separate multivariable linear regression models, mechanical dispersion, GLS, and LVEF were all significantly associated with hs-cTnT concentrations (*Table 4*). In contrast, only mechanical dispersion was associated with hs-cTnT concentrations when all three echocardiographic indices were included in the same model (Supplementary material online, *Table S7*). For NT-proBNP, mechanical dispersion and LVEF were both associated with increasing concentrations when adjusting for demographic variables and CV risk factors (*Table 4*). These associations remained after adjusting for all three echocardiographic indices in the same model (Supplementary material online, *Table S7*).

Discussion

The principal findings from this large population-based study were that CV risk factors in the early forties are associated with increased mechanical dispersion two decades later and that mechanical dispersion is independently associated with cardiac biomarkers in the mid-sixties. Hence, our study lends support to the concept of mechanical dispersion as an early echocardiographic index of subclinical myocardial injury and dysfunction.

LV mechanical dispersion appears to be a promising echocardiographic index across different populations with CV disease. Increased mechanical dispersion reflects a heterogeneous contraction pattern that has been postulated to reflect pathology in the electrical conduction pathway or mechanical changes in the myocardium.[26] In line with this, mechanical dispersion has previously been found associated with ventricular arrhythmias and sudden cardiac death in patients with different types of established CV disease.[7,27–29] Recently, a Danish general population study also reported that mechanical dispersion predicted cardiac death, but not non-cardiac death, during median 11 years follow-up.[6] We have previously also found established CAD and hypertension to be independently associated with high mechanical dispersion values in subjects 62–65 years old from the general population.[5] We now validate and extend these observations by demonstrating an association between CV risk factors in early mid-life and mechanical dispersion obtained over 20 years later. We also demonstrate independent associations between mechanical dispersion and NT-proBNP and hs-TnT concentrations, which are established cardiac biomarkers reflective of myocardial injury and dysfunction. Hence, mechanical dispersion could have the potential as a novel echocardiographic risk index across different populations, including subjects with sub-clinical CV disease. Still, there are a number of questions for mechanical dispersion that need to be resolved prior to widespread clinical use, including the pathobiology underlying the prognostic potential of mechanical dispersion in large population-based cohorts.

The current model for mechanical dispersion postulates that mechanical dispersion reflects a risk of future ventricular arrhythmias. However, the pathobiology underlying the increased risk of arrhythmias is not clear. Other groups have proposed that mechanical dispersion may reflect myocardial fibrosis. Pertinent to this point, mechanical dispersion has been found associated with myocardial fibrosis as assessed by cardiac magnetic resonance imaging and late gadolinium enhancement (LGE) in patients with hypertrophic cardiomyopathy.[7] Supporting a model of mechanical dispersion as an echocardiographic index of cardiac fibrosis, mechanical dispersion also correlated with LGE-quantified focal myocardial fibrosis in patients with first-time ST-segment elevation myocardial infarction.[30] The previously identified associations between increasing mechanical dispersion and established CAD and hypertension, which both are known to contribute to LV remodelling, also support a model of mechanical dispersion as reflective of cardiac fibrosis. We now add to this information by demonstrating independent associations between mechanical dispersion and established cardiac biomarkers of myocardial injury and dysfunctions in a population of subjects in the mid-sixties recruited from the general population primarily without established CV disease. In a study assessing the prognostic value of mechanical dispersion and NT-proBNP in stable CAD patients, mechanical dispersion had incremental prognostic value to LVEF and GLS.[31] These results support that mechanical dispersion may provide incremental information on cardiac structure and function compared to established echocardiographic indices, but this will need to be tested in more cohorts with prospective clinical endpoints, including in the general population. Prior to widespread clinical use in the general population, we will also need to know more about the appropriate therapeutic interventions to start in subjects with high mechanical dispersion. Currently, this is not known, but based on the model of mechanical dispersion as reflective of myocardial fibrosis, treating common risk factors throughout adult life will probably attenuate an increase in mechanical dispersion values in later life. Our results provide some indirect support for such a strategy as we now report associations between common CV risk factors in early mid-life (age 40 years) and mechanical dispersion measured more than 20 years later. This also relates to obesity as we and others identify high BMI as associated with increased mechanical dispersion values,[6] including when adjusted for established CAD in our multivariable statistical model. However, whether mechanical dispersion adds information to the use of common risk stratification models to predict incident CV disease in the general population is not known, and this will also need to be established before introducing mechanical dispersion as an echocardiographic index to screen for sub-clinical CV disease in the general population. Of note, we did not find risk factors for vascular disease, e.g., smoking, diabetes mellitus, and arterial hypertension, to be associated with mechanical dispersion. This result will need validation in other cohorts, but supports a model of mechanical dispersion being more reflective of LV remodelling and fibrosis than of CAD per se.

Strengths and limitations

A major strength of this study is the high number of participants with available echocardiograms as well as analyses of hs-cTnT and NT-

Table 4 **Associations between LV mechanical dispersion, GLS and EF, and the biomarkers hs-cTnT and NT-proBNP, performed with the echocardiographic indices in separate multivariable linear regression analyses**

Variables	Model 1		Model 2		Model 3	
	B (95% CI)	*P*-value	B (95% CI)	*P*-value	B (95% CI)	*P*-value
hs-cTnT (dependent variable)						
LV mechanical dispersion, per 10 ms increase	0.040 (0.024 to 0.057)	<0.001	0.032 (0.017 to 0.046)	<0.001	0.029 (0.015 to 0.043)	<0.001
LV GLS, per 1% increase	0.046 (0.036 to 0.055)	<0.001	0.020 (0.011 to 0.028)	<0.001	0.012 (0.004 to 0.021)	0.006
LV EF, per 5% increase	-0.087 (-0.109 to -0.066)	<0.001	-0.047 (-0.067 to -0.027)	<0.001	-0.026 (-0.045 to -0.006)	0.010
NT-proBNP (dependent variable)						
LV mechanical dispersion, per 10 ms increase	0.030 (0.010 to 0.051)	0.004	0.033 (0.013 to 0.053)	0.001	0.024 (0.003 to 0.045)	0.022
LV GLS, per 1% increase	-0.017 (-0.029 to -0.005)	0.004	-0.005 (-0.018 to 0.007)	0.39	-0.003 (-0.015 to 0.009)	0.65
LV EF, per 5% increase	-0.022 (-0.049 to 0.005)	0.12	-0.041 (-0.068 to -0.013)	0.004	-0.029 (-0.057 to -0.001)	0.044

Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, adjusted for age, sex, study site, higher education level, body mass index, eGFR, total cholesterol, HDL cholesterol, diabetes mellitus, hypertension, coronary artery disease, statin therapy, and current smoking.
B, unstandardized coefficient; CI, confidence interval; EF, ejection fraction; GLS, global longitudinal strain; hs-cTnT, high-sensitivity cardiac troponin T; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

proBNP concentrations. The echocardiographic recordings and analyses were performed by several researchers and therefore represent a real-life scenario close to a clinical setting. We could link data from two age-specific studies, allowing us to assess the associations between variables at age 40 with mechanical dispersion two decades later. Survival bias may be present, as deceased participants of the Age 40 Program could not be included in the ACE 1950 cohort. Selection bias is additionally a limitation, as we do not have information on the individuals who refused to participate in the studies. We used peak R as the start of the cardiac circle as this was automatically detected by the software and because peak R more consistently can be detected compared to the start of QRS. We acknowledge that the start of QRS complex could have been chosen, but we do not believe this would have influenced our results. As we currently do not have follow-up data with endpoints for the ACE 1950 Study population, we are not able to investigate whether mechanical dispersion is associated with sudden cardiac death or ventricular arrhythmias in a general population. We plan to investigate this in the future.

Conclusion

In a large community-based cohort, we demonstrate that established CV risk factors in early adulthood are associated with worse mechanical dispersion in mid-life, and that mechanical dispersion is cross-sectionally associated with biomarkers of sub-clinical myocardial injury and dysfunction in middle age.

Lead Author Biography

Erika Nerdrum Aagaard, MD, has a medical degree from 2007 from The Jagiellonian University, Krakow, Poland. She is currently finishing her PhD at the University of Oslo and the Akershus University Hospital where she also works as a cardiology resident. She is passionate about cardiology in general and echocardiography specifically, with a main research focus on strain imaging and mechanical dispersion.

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Conflict of interest: T.O. has served on advisory boards for Abbott Diagnostics, Roche Diagnostics and Bayer and has received research support from Abbott Diagnostics, Novartis, Roche Diagnostics, Singulex and SomaLogic via Akershus University Hospital, and speaker's or consulting honoraria from Roche Diagnostics, Siemens Healthineers and CardiNor. H.R. has received personal fees from Novartis and Thermo Fischer BRAMS, CardiNor and SpinChip. T.B. has received speaker fees from Bayer, Boehringer Ingelheim, BMS and Pfizer (non-related to the submitted work). E.N.A. and the remaining co-authors have nothing to disclose.

Data Availability

The data set used in this study is not publicly available; the Data Protection Authority approval and patient consent do not allow for such publication. However, the study group welcomes initiatives for cooperation, and data access may be granted upon application. More information is available on the study website (http://www.ace1950.no).

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