Mechanical Dispersion as Marker of Left Ventricular Dysfunction and Prognosis in Stable Coronary Artery Disease

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Supplementary Table 1: Determinants of deformation parameters

	Mechanical dispersion		Global longitudinal strain	
	B (95% CI)	***P* value**	**B (95% CI)**	***P* value**
Age, yrs	0.49 (0.27-0.72)	<0.001	0.02 (-0.02-0.06)	0.409
Male sex	0.23 (-4.95-5.41)	0.929	1.27 (0.36-2.17)	0.006
Prior CABG	6.85 (1.40-12.29)	0.014	1.57 (0.62-2.53)	0.001
Current smoking	-0.10 (-5.12-4.92)	0.969	0.92 (0.04-1.81)	0.042
Diabetes	3.12 (-5.27-11.50)	0.464	1.70 (0.23-3.18)	0.024
BSA, kg/m^2	5.84 (-7.61-19.29)	0.392	2.70 (0.40-5.00)	0.022
Heartrate, beats/minute	-0.32 (-0.54 to -0.10)	0.004	0.03 (-0.01-0.07)	0.089
EF, %	-0.15 (-0.41 to -0.11)	0.251	-0.10 (-0.15 to -0.06)	<0.001
Abbott hs-cTnI, ng/L	6.61 (4.44-8.79)	<0.001	0.83 (0.43-1.24)	<0.001
Roche NT-proBNP, ng/L	4.33 (2.69-5.97)	<0.001	0.39 (0.07-0.70)	0.016
eGFR, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	-0.23 (-0.36 to -0.11)	0.001	-0.01 (-0.03-0.01)	0.411

Values of hs-cTnI and NT-proBNP are log-transformed.

B, unstandardized coefficients; CI, confidence interval; CABG, coronary artery bypass grafting; BSA, body surface area; EF, ejection fraction; hs-cTnI, high-sensitivity troponin I; NT-proBNP, amino-terminal pro B-type natriuretic peptide; eGFR, estimated glomerular filtration rate.

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Abstract

Purpose: Assessment of global longitudinal strain (GLS) is superior to ejection fraction (EF) in evaluation of left ventricular (LV) function in patients with stable coronary artery disease (CAD). However, the role of mechanical dispersion (MD) in this context remains unresolved. We aimed to evaluate the potential role of MD as a marker of LV dysfunction and long-term prognosis in stable CAD.

Methods: EF, GLS and MD were assessed in 160 patients with stable CAD, one year after successful coronary revascularization. Serum levels of high-sensitivity cardiac troponin I (hs-cTnI) and amino-terminal pro B-type natriuretic peptide (NT-proBNP) were quantified as surrogate markers of LV dysfunction. The primary endpoint was defined as all-cause mortality, the secondary endpoint was defined as the composite of all-cause mortality and hospitalization for acute myocardial infarction or heart failure during follow-up.

Results: Whereas no associations between EF and the biochemical markers of LV function were found, both GLS and MD correlated positively with increasing levels of hs-cTnI (R=0.315, $P<0.001$ and R=0.442, $P<0.001$, respectively) and NT-proBNP (R=0.195, $P=0.016$ and R=0.390, $P<0.001$, respectively). Median MD was 46 ms (interquartile range [IQR]: 37-53) and was successfully quantified in 96% of the patients. During a median follow-up of 8.4 (IQR: 8.2-8.8) years, 14 deaths and 29 secondary events occurred. MD was significantly increased in non-survivors, and provided incremental prognostic value when added to EF and GLS. NT-proBNP was superior the echocardiographic markers in predicting adverse outcome.

Conclusions: MD may be a promising marker of LV dysfunction and adverse prognosis in stable CAD.

Keywords: Stable coronary artery disease; speckle tracking echocardiography; myocardial strain; mechanical dispersion; high-sensitivity troponin I; amino-terminal pro-B-type natriuretic peptide.

Introduction

Coronary artery disease (CAD) is regarded as the leading cause of left ventricular (LV) dysfunction and subsequent development of heart failure in the western world [1]. The subgroup of patients with stable CAD is heterogenic, including stabilized patients after an acute coronary syndrome, often treated with coronary revascularization. Although long-term prognosis in stable CAD has gradually improved over the last decades as a result of more cost-effective medical treatment, the prevalence is increasing due to an aging population, increased prevalence of risk factors and more sensitive diagnostic tools [2].

A resting transthoracic echocardiogram is recommended in all patients with suspected stable CAD for evaluation of cardiac structure and function [2]. LV dysfunction, most commonly quantified by measurement of LV ejection fraction (EF), is the most important predictor of outcome in these patients. Whereas EF is closely linked to mortality in patients with moderate and severe LV dysfunction, no such association is applicable for normal or mild impairment of LV function [3]. Although most patients with stable CAD have normal EF, the risk of *de novo* heart failure development is not negligible, despite standard medical therapy [4]. In this respect, improved identification of stable CAD patients with increased risk of adverse outcome is of clinical importance.

Myocardial strain by two-dimensional speckle tracking echocardiography (2D-STE) has emerged as a validated tool for evaluation of LV function [5,6]. Global longitudinal strain (GLS) is established as a robust parameter for early identification of LV dysfunction [7], and is superior to EF in prediction of adverse outcomes in diverse cardiac disorders [8]. In patients with clinically suspected stable angina pectoris, GLS improves the diagnostic performance and identification of high-risk patients [9].

LV mechanical dispersion (MD) is a novel application of 2D-STE that quantifies the contraction heterogeneity in 16 LV segments [10]. Increased MD is associated with malignant

arrhythmias in patients with ischemic heart disease and hypertrophic cardiomyopathy [11]. Furthermore, MD has incremental diagnostic value to GLS when identifying patients with significant CAD [12]. Thus, we hypothesized that MD might be a promising marker of subtle myocardial dysfunction and long-term prognosis in patients with stable CAD.

Methods

Study design and population

This prospective study was conducted between 2008 and 2009 in a single tertiary coronary care center, and includes 160 patients referred to a follow-up echocardiography approximately 1 year after successful coronary revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) [13]. Exclusion criteria were valvular disease, ongoing atrial fibrillation, left bundle branch block, ventricular paced rhythm and recurrent angina or cardiovascular events between revascularization and study inclusion.

Echocardiographic studies

Echocardiographic examinations were performed with a Vivid 7 scanner (GE Ultrasound, Horten, Norway) and analyzed off-line using EchoPAC version 12 (GE Ultrasound). Images from three apical planes (four-chamber, two-chamber and long-axis) were obtained and used for strain analyses. The median frame rate was 63 (interquartile range [IQR]: 59-71) frames per second. EF was assessed by the Simpson biplane method [6], and body surface area (BSA) was calculated using the Mosteller equation [14]. All patients underwent coronary angiography by Judkins technique 346 (IQR: 281-376) days prior to follow-up, 73% due to non-ST elevation acute coronary syndrome and 27% due to stable angina pectoris.

Longitudinal strain was measured using a 16-segment LV model, and GLS was obtained by averaging all peak systolic strain values [15]. Peak strain was defined as the maximum

absolute value of peak negative strain during systole, including post-systolic shortening, if present. End of systole was defined by the aortic valve closure in apical long-axis view. The operator manually adjusted segments that failed to track, and segments that subsequently failed to track were excluded. Patients were excluded from strain analyses if more than two segments failed to track in a single view [6]. Contraction duration was calculated as the time from ECG onset of the Q/R-wave to peak strain in all 16 LV segments, and MD was defined as the standard deviation of the contraction durations in the same 16 LV segments (Figure 1) [16,10]. Assessment of GLS and MD was performed by a single observer (B.K) and blinded to other patient data during reevaluation of the echocardiographic examinations in conjunction with the current study.

Feasibility and variability analysis

Measurement of GLS and MD was repeated in 10 randomly selected patient records, and showed intra-observer intra-class correlation coefficients of 0.84 (95% confidence interval [CI] 0.27-0.96; $P<0.001$) and 0.88 (95% CI 0.50-0.97; $P<0.001$). Inter-observer analyses were performed in 10 randomly selected patient records by a second observer (E.N.A), and intra-class correlation coefficients of 0.90 (95% CI 0.43-0.98; $P<0.001$) and 0.93 (95% CI 0.73-0.98; $P<0.001$) were found for GLS and MD, respectively.

Biochemical analysis

Peripheral venous blood was collected the same day as the echocardiographic recordings, and serum aliquots were stored at -70 °C until analysis. The Roche amino-terminal pro-B-type natriuretic peptide (NT-proBNP) assay was analyzed on a Modular E170 platform using the Elecsys reagents, with a limit of detection (LoD) of 5 ng/L, and a 97.5th percentile cutoff of 263 ng/L. The inter-assay CV was 3.1% at a concentration of 46 ng/L and 2.7% at a concentration

of 125 ng/L. The Abbott hs-cTnI assay was measured on ARCHITECT STAT and had a LoD of 1.9 ng/L, a 99th percentile in healthy individuals of 26 ng/L, and a 10% CV at 4.7 ng/L [17]. Renal function was evaluated by the estimated glomerular filtration rate (eGFR) [18]. The investigational assays were commercially available and supplied by the respective manufacturers, which had no role in the preparation of the manuscript.

Study outcomes

The primary endpoint was all-cause mortality, defined as time to death irrespective of cause. The secondary endpoint was defined as the composite of all-cause mortality and hospitalization for recurrent acute myocardial infarction or new-onset heart failure. Follow-up was obtained by review of the patient's hospital charts or telephone interviews with the patients or relatives, and no patients were lost to follow-up.

Statistical analysis

The data are presented as medians and IQR. Categorical and discrete variables are presented as counts and percentages. Groups were compared with the Mann-Whitney U test or χ^2-tests where appropriate. The correlations between echocardiographic findings and log-transformed biomarker levels were estimated by the Pearson method. Variables associated with either GLS or MD were examined by first order linear regression analysis and are presented if $P<0.1$. The unadjusted prognostic accuracy of the respective echocardiographic methods in prediction of both endpoints was determined by area under the ROC curve (AUCs). In the survival models, the echocardiographic parameters were evaluated both as continuous and dichotomous variables. EF, GLS and MD were dichotomized at 53 %, -18 % and 64 ms, respectively, using previously defined reference levels [6,16,19,20]. Cox proportional hazards regression models were generated to test the relationship between levels of echocardiographic markers and time

to events. Kaplan-Meier survival curves were generated and associations between the respective echocardiographic parameters and endpoints were compared by the log-rank test. AUCs were compared by the DeLong test [21]. The incremental value of adding MD to the respective echocardiographic and biochemical parameters was investigated using continuous net reclassification improvement (NRI) and integrated discrimination index [22]. All statistical tests were 2-sided, and a significance level of 0.05 was used. All statistical analyses were performed using either SPSS version 25 (SPSS Inc.), MedCalc Statistical Software version 18.2.1 or R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

The authors are solely responsible for study design, all analyses, and drafting and editing of the manuscript.

Results

Patient characteristics

Baseline characteristics for all 160 patients are presented in Table 1. The study included 118 males (74 %) and all patients had asymptomatic stable CAD at the time of inclusion. Most patients were on medical therapy including antiplatelet medication, lipid lowering drugs and beta blockers. Either angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) were used by 48 patients (30 %). The study included 15 (9.4 %) patients with renal dysfunction, defined as eGFR<60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$.

Echocardiographic evaluation and markers of LV dysfunction

The main echocardiographic findings are presented in Table 1. In total, 153 (96 %) patients had technically adequate echocardiograms for speckle tracking analysis and 97 % of the myocardial segments could be analyzed. Overall, the majority of the cohort displayed a normal EF, with 130 (81 %) of the patients with levels above 53 %. GLS was slightly reduced, with 69 patients

(44 %) within the normal range below -18%. For MD, 138 patients (86 %) were within the normal range below 64 ms. In univariate analysis, MD was significantly associated with age, heart rate, and kidney function, while GLS was associated with male sex, diabetes, current smoking and BSA (Supplementary Table 1). The correlation coefficient between GLS and MD was 0.254 (p=0.002). Both deformation parameters were associated with prior CABG.

Levels above detection limit of hs-cTnI and NT-proBNP were observed in 112 patients (70%) and 159 patients (99 %), respectively. The proportion of patients with hs-cTnI levels above the 99th percentile was 1.9 %, while 17 % of the patients had levels of NT-proBNP above the 97.5th percentile. As opposed to EF, both GLS and MD were associated with increasing hs-cTnI and NT-proBNP levels (Table 2 and Figure 2). Only MD remained significantly associated with rising biomarker levels after adjustment for other echocardiographic parameters (Table 2). Collinearity was not observed.

Prediction of long-term prognosis

The median follow-up period was 8.4 (IQR: 8.2-8.8) years. There were 14 deaths, 12 hospitalizations for recurrent AMIs and 3 hospitalizations for new onset heart failure during the follow-up period. Non-survivors were older, had a higher prevalence of diabetes, lower levels of eGFR and higher BMI. Speckle tracking echocardiography showed a trend towards more pronounced MD in non-survivors vs. survivors (median 54 [IQR: 45-72] ms vs. median 45 [IQR: 37-53] ms; P=0.012) and in patients with composite endpoint vs. no composite endpoint (median 52 [IQR: 42-64] ms vs. median 45 [IQR: 36-53] ms; P<0.01). No such differences were found for EF and GLS. MD remained associated with adverse outcome after adjusting for all ECG parameters. Both hs-cTnI and NT-proBNP were significantly elevated among non-survivors and patients in the composite endpoint group (P<0.01; Figure 3).

The unadjusted prognostic accuracies for the echocardiographic and biochemical parameters are presented in Table 3. Only NT-proBNP was superior to MD in prediction of all-cause mortality, while MD, hs-cTnI and NT-proBNP showed similar abilities in prediction of composite endpoint. Adding MD to EF, GLS, and hs-cTnI provided significant improvements in risk stratification, but not when MD was added to NT-proBNP (Table 4). Among the echocardiographic parameters, only MD was associated with all-cause mortality and the composite endpoint (Table 5). MD remained a significant predictor for both endpoints when adjusting for both EF and GLS. Kaplan-Meier curves depicting the cumulative incidence of all-cause mortality and the composite endpoint are shown in Figure 4. A MD>64 ms identified individuals with a poor prognosis, both for all-cause mortality (log-rank $P<0.01$), as well as the composite endpoint (log-rank $P=0.014$).

Discussion

The present study demonstrates that novel deformation parameters obtained by 2D-STE are superior to EF for determination of LV function and long-term prognosis in patients with stable CAD. Although both GLS and MD were related to serum markers of LV dysfunction, the association was most prominent for MD. In addition, MD was the only echocardiographic parameter that provided significant prognostic information in this study. NT-proBNP was superior to all other markers in the prediction of all-cause mortality.

Traditionally, EF has been the established echocardiographic parameter for quantification of cardiac function and prognostic evaluation. However, the association between EF and mortality is most prominent for EF below 45% [3]. As most patients with stable CAD have a normal or subnormal EF and an overall good prognosis, other parameters should be used for prognostic evaluation in this patient group. A systematic review of 16 studies including

5721 patients concluded that GLS provided superior prognostic information to that of EF, in patients with mild LV dysfunction of diverse etiologies [9].

A recent study demonstrated how EF could be maintained in the left ventricle with increased wall thickness or reduced diameter, despite reductions in global strain parameters [23]. A significant reduction in GLS could be compensated by a small increase of global circumferential strain, resulting in an unaltered EF. This may be the fundamental basis for the observed superiority of GLS to EF in evaluation of LV function in patients with preserved EF [24].

MD is a novel deformation parameter which reflects contraction heterogeneity, with a promising potential for prediction of ventricular arrhythmias in patients with ischemic heart disease, independently of EF and QRS interval [25]. Increased MD may also reflect myocardial scarring and interstitial collagen depositions, which in turn could give rise to local electromechanical delays [19,20]. As an index of contraction discordance of the respective LV segments, MD could potentially give additive information of subtle LV dysfunction at an early stage [26].

While the limit for increased MD is still being debated, current guidelines recommend decision limits for EF and GLS at 53% and -18%, respectively [6]. In our study, a cutoff limit at -18% implies LV dysfunction in 55% of the patients. GLS was associated with diabetes, smoking and increased BSA, which are associated with the extent of coronary artery disease [27]. This could explain the large portion of patients with subnormal GLS values. Although earlier studies have suggested a limit for increased MD at 70 ms [16], recent data from healthy volunteers suggest that 64 ms might be a more precise limit in an elderly patient cohort [20]. In our population with stable CAD patients, the latter decision limit seems to provide prognostic information. In univariate analyses, MD was associated with increasing age and reduced kidney function, both factors which are associated with adverse outcome in CAD patients [28]. As only

9% of the patients displayed MD above 64 ms and MD at this cutoff level was superior to GLS in prediction of long-term prognosis, MD may be a more specific prognostic parameter than GLS.

Although not yet included in the guidelines, the incremental prognostic value of cardiac biomarkers in CAD patients is well documented. Increased levels of both NT-proBNP and cardiac troponins, measured with high-sensitivity assays, are significantly associated with impaired LV function and clinical outcomes in patients with stable CAD and in the general population [29,30]. Interestingly, a prognostic discrimination for these biomarkers can be observed even within the normal range. NT-proBNP levels correlate with both age and other traditional risk factors of CV disease, and provide prognostic information beyond that of established risk markers. Further, increased levels of NT-proBNP are associated with history of myocardial infarction, 3-vessel disease and signs of impaired systolic function in patients with stable CAD. Hence, the prognostic value of NT-proBNP might be related to risk factors associated with asymptomatic LV dysfunction [31].

Chronic elevation of hs-cTn and NT-proBNP levels are considered as markers of increased myocardial stress which in turn could develop into diffuse myocardial fibrosis, hypertrophy and ventricular dysfunction [32]. These processes are strongly associated with the risk of heart failure, ventricular arrhythmias and adverse outcome. Interestingly, our results indicate that MD display similar characteristics as NT-proBNP and hs-cTnI, as opposed to EF. Several factors influence a stable CAD population, which may explain the modest correlations found between biomarkers and deformation parameters. However, our findings are in line with previous studies [33,34]. Similar to NT-proBNP, age and reduced kidney function seems to be important determinants of MD. The fact that they share these important determinants could partly explain why MD did not add prognostic information to NT-proBNP. A recent study of

a healthy population showed that aging leads to a progressive rise in MD [20]. Nevertheless, both GLS and MD correlate with myocardial fibrosis [19,35].

Clinical implications

Although MD provides superior prognostic information to EF and GLS, and GLS is the more sensitive marker of LV dysfunction, the incremental value of cardiac biomarkers should be emphasized. Elevated levels of both NT-proBNP and hs-cTn provide additive prognostic information in patients with stable CAD. Recently, NT-proBNP and hs-cTnT together with several clinical parameters have been incorporated in a novel risk score, in order to improve risk stratification in stable CAD patients [36]. In our study, NT-proBNP was superior to all echocardiographic parameters for prognostic evaluation. To our best knowledge, no previous studies have either compared the diagnostic and prognostic value between biochemical markers and echocardiographic parameters in patients with stable CAD. The use of deformation parameters in a multimarker approach should be examined in future studies with larger sample sizes.

There is evidence supporting beneficial effects of ACE-inhibitors in subgroups of stable CAD patients, despite preserved EF [37]. Patients with subclinical LV dysfunction in combination with elevated cardiac biomarkers may be tentative candidates to benefit from statins, ACE-inhibitors or other preventive strategies. Current guidelines recommend transthoracic echocardiography to assess EF and wall motion abnormalities, while cardiac troponins and natriuretic peptides are still not a part of standard follow-up in these patients [2]. Although GLS is mentioned as a useful tool in the assessment of stable CAD patients, our results indicate that MD could also be assessed when performing deformation analyses.

Study limitations

This is an observational study and may be prone to inherent bias. The current study performed echocardiographic examinations and obtained blood samples one year after successful coronary revascularization, and is consequently applicable only to this patient group. It is a heterogenic cohort of patients, including new onset angina and previous myocardial infarctions. Nevertheless, we believe that our cohort reflects common clinical practice. Due to the relatively small sample size and few endpoints, we consider our study to be exploratory, and the results should be confirmed in larger cohorts. All myocardial indexes analyzed in this study has limitations in the detection of LV dysfunction, making risk stratification in this cohort challenging. The study population is at low risk for malignant arrhythmias, and the study was not designed to evaluate arrhythmic events. Finally, strain measurements, as all echocardiographic measurements, are dependent on good image quality and operator experience.

Conclusions

NT-proBNP is the superior marker for prognostic evaluation in patients with stable CAD. MD correlates with established markers of subtle LV dysfunction and give incremental prognostic information to other echocardiographic markers. Further studies are needed to evaluate the role of MD in a multiparameter approach.

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Conflicts of interest

J.G has received lecture fees from Abbott laboratories.

Ethical standards

The Regional Ethics Committee approved the study, and all subjects provided written, informed consent.

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Table 1: Baseline characteristics

Characteristics	All patients (n=160)
Age, yrs	59 (52-67)
Male sex	118 (73.8)
Risk factors	
Prior myocardial infarction	29 (18)
Current smoking	46 (29)
Diabetes	14 (8.8)
Hypertension	65 (41)
Clinical findings	
BMI, kg/m^2	27 (25-29)
BSA, m^2	2.0 (1.9-2.1)
Systolic blood pressure, mm Hg	144 (127-160)
Diastolic blood pressure, mm Hg	81 (71-90)
Heartrate, beats/min	61 (53-69)
Echocardiographic data	
EF, %	63 (56-68)
GLS, %	-17.7 (-19.3 to -16.5)
MD, ms	46 (37-54)
EDV, ml	106 (89-127)
ESV, ml	40 (30-52)
Laboratory data	
Hs-cTnI, ng/L	3.2 (1.7-5.0)
NT-proBNP, ng/L	74 (34-205)
eGFR, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	88 (72-99)
Medical therapy	
ACEI/ARB	48 (30)
Beta-blockers	129 (81)
Lipid-lowering drug	147 (92)
Aspirin or other antiplatelet medication	157 (98)
ECG data	
QRS duration, ms	94 (87-100)

QTc interval, ms	417 (398-439)
T wave changes, %	58 (36)
Q waves, %	13 (8.1)
Procedural data*	
PCI	126 (79)
CABG	34 (21)
One vessel disease	84 (53)
Two or more vessel disease	76 (48)
Total vessel occlusion	26 (16)

Values are median (IQR) and n (%). *Approximately one year prior to main examination.

BMI, body mass index; BSA, body surface area; EF, ejection fraction; GLS, global longitudinal strain; MD, mechanical dispersion; EDV, end-diastolic volume; ESV, end-systolic volume; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Table 2: Relationships with hs-cTnI and NT-proBNP

	Multiple linear regression		Final model *	
	B (95% CI)	***P* value**	**B (95% CI)**	***P* value**
Abbott hs-cTnI				
EF, per 5 % decrease	0.03 (-0.01-0.06)	0.154		
GLS, per 1 % increase	0.05 (0.03-0.08)	<0.001		
MD, per 10 ms increase	0.13 (0.09-0.17)	<0.001	0.13 (0.09-0.18)	<0.001
Roche NT-proBNP				
EF, per 5 % decrease	0.02 (-0.03-0.07)	0.420		
GLS, per 1 % increase	0.04 (0.02-0.18)	0.016		
MD, per 10 ms increase	0.15 (0.10-0.21)	<0.001	0.16 (0.10-0.22)	<0.001

Values of hs-cTnI and NT-proBNP are log-transformed. Abbreviations as in Table 1.

*Adjusted for all other covariates in the table using forward regression.

Table 3: Prediction of long-term prognosis

	AUC	95% CI	*P* value	*P* value vs. MD
All-cause mortality				
EF, %	0.56	0.38-0.74	0.493	0.384
GLS, %	0.59	0.43-0.75	0.263	0.285
MD, ms	0.71	0.55-0.87	0.009	NA
Hs-cTnI, ng/L	0.72	0.56-0.88	0.007	0.375
NT-proBNP, ng/L	0.86	0.73-0.99	<0.001	0.049
Composite endpoint				
EF, %	0.52	0.39-0.65	0.742	0.023
GLS, %	0.55	0.44-0.67	0.370	0.036
MD, ms	0.69	0.58-0.79	<0.001	NA
Hs-cTnI, ng/L	0.67	0.55-0.78	0.005	0.750
NT-proBNP, ng/L	0.67	0.54-0.79	0.012	0.622

AUC, area under the receiver operating characteristic curve; other abbreviations as in Table 1.

Table 4: Incremental prognostic value of MD

	Continuous NRI	IDI
All-cause mortality		
EF, %	0.613 (0.062-1.164)*	0.109 (0.002-0.215)*
GLS, %	0.574 (0.022-1.125)*	0.087 (0.003-0.171)*
Hs-cTnI, ng/L	0.608 (0.057-1.159)*	0.107 (0.006-0.208)*
NT-proBNP, ng/L	0.352 (-0.211-0.914)	0.098 (-0.003-0.198)
Composite endpoint		
EF, %	0.447 (0.018-0.876)*	0.100 (0.030-0.171)†
GLS, %	0.593 (0.193-0.992)†	0.080 (0.023-0.137)†
Hs-cTnI, ng/L	0.495 (0.084-0.905)*	0.092 (0.028-0.157)†
NT-proBNP, ng/L	0.333 (-0.078-0.745)	0.060 (0.004-0.116)*

Abbreviations as in Table 1. NRI, net reclassification improvement, IDI, integrated discrimination index. *P<0.05. †P<0.01

Table 5: Multivariate analysis; effects of LV EF, GLS and MD on long-term prognosis

	Hazard ratio (95% CI)	
	Unadjusted	**Final model ***
All-cause mortality		
EF, per 5 % decrease	0.81 (0.58-1.14)	
GLS, per 1 % increase	1.19 (0.97-1.45)	
MD, per 10 ms increase	1.93 (1.33-2.79)†	1.91 (1.32-2.76)†
Composite endpoint		
EF, per 5 % decrease	1.00 (0.80-1.23)	
GLS, per 1 % increase	1.08 (0.94-1.25)	
MD, per 10 ms increase	1.62 (1.25-2.09)†	1.68 (1.29-2.20)†

Abbreviations as in Table 1. *Adjusted for all covariates in the table using forward conditional regression. †$P<0.01$.

Figure legends

Figure 1: Biochemical markers and deformation parameters in representative patients.

White horizontal lines indicate contraction duration, defined as time from ECG onset of Q/R to peak negative strain. MD was defined as the standard deviation of contraction duration in 16 LV segments. Despite normal EF in both patients, the patient from the survivor group displays normal biochemical markers and deformation parameters (A), while the patient from the non-survivor group displays pathological deformation parameters and increased biochemical markers (B). ECG, electrocardiogram; LV, left ventricular; Hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; GLS, global longitudinal strain; MD, mechanical dispersion; EF, ejection fraction.

Figure 2: Relationships between biochemical markers and echocardiographic parameters.

Biomarker levels were log-transformed and correlations were estimated by the Pearson method. Abbreviations as in Figure 1.

Figure 3: Range of biochemical markers and echocardiographic parameters depending on clinical outcome.

Range of EF (A), GLS (B), MD (C), hs-cTnI (D) and NT-proBNP (E) depending on clinical outcome. *P=0.05. †P<0.01. Abbreviations as in Figure 1.

Figure 4: Prediction of adverse outcome.

Kaplan-Meier curves demonstrating the cumulative incidence of all-cause mortality and the composite endpoint in the total patient cohort, according to dichotomized levels of the different biochemical and echocardiographic parameters. EF, GLS and MD are dichotomized at 53 %, -18% and 64 ms, while hs-cTnI and NT-proBNP are dichotomized at 26 ng/L and 263 ng/L, respectively. Abbreviations as in Figure 1.