Multimodality imaging in the characterization and risk-stratification of cardiac disease and CRT recipients

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Prognostic implications of global, left ventricular myocardial work efficiency before cardiac resynchronization therapy

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) restores mechanical efficiency to the failing left ventricle (LV) by resynchronization of contraction. Global, LV myocardial work efficiency can be quantified non-invasively with echocardiography, although the prognostic implication of this parameter remains unexplored. The objective was to relate global, LV myocardial work efficiency before CRT to long-term prognosis.

Methods: Data were analyzed from an ongoing registry of heart failure patients with class I indications for CRT according to contemporary guidelines. Global, LV myocardial work efficiency was defined as the ratio of the constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments, as a percentage ((constructive work/(constructive work + wasted work)) x 100%). It was derived from speckle tracking strain echocardiography and non-invasive blood pressure measurements, taken before CRT implantation. Patients were dichotomized according to the baseline, median global, LV myocardial work efficiency (75%; interquartile range 66-81%).

Results: A total of 153 patients (mean age 66±10 years, 72% male, 48% ischemic heart disease) were analyzed. After a median follow-up of 57 months (interquartile range 28-76 months), 31% of patients died. CRT recipients with less efficient energetics at baseline (global, LV myocardial work efficiency <75%) demonstrated lower event rates than patients with more efficient baseline energetics (global, LV myocardial work efficiency ≥75%) (log-rank test, P=0.029). On multivariable analysis, global LV myocardial work efficiency <75% pre-CRT was independently associated with a decreased risk of all-cause mortality (hazard ratio 0.48, 95% confidence interval 0.25-0.92; P=0.027), suggesting that the potential for improvement in LV efficiency is an important mechanism in CRT benefit.

Conclusions: Global, LV myocardial work efficiency can be derived non-invasively from speckle tracking strain echocardiography data and non-invasive blood pressure recordings. A lower global, LV myocardial work efficiency before CRT, is independently associated with improved long-term outcome.

INTRODUCTION

Cardiac work refers to the amount of mechanical energy which is expended in the process of left ventricular (LV) contraction and relaxation.[1] Electrical conduction disturbances strongly influence LV work. In the presence of a left bundle branch block (LBBB), the interventricular septum is activated early and contracts before aortic valve opening. The early contraction of the septum thereby stretches the LV lateral wall before it has contracted, and when the lateral wall is activated late, the interventricular septum is stretched, leading to inefficient cardiac work (without LV ejection of blood or stroke volume).[2] Cardiac resynchronization therapy (CRT), an effective therapy in selected heart failure patients,[3] restores mechanical efficiency to the failing LV by resynchronization of contraction. The less efficiently the LV operates at baseline, the greater the potential for recovery of efficient LV work with CRT. Whether a greater reserve of potentially recoverable global, LV myocardial work efficiency before CRT translates into improved outcome, is unknown. Global, LV myocardial work efficiency can be quantified non-invasively with a novel, echocardiography-based technique.[4] Speckle tracking strain echocardiography data are combined with non-invasive blood pressure recordings to calculate segmental cardiac work and subsequently, the global, LV myocardial work efficiency.[2] Both preclinical and clinical studies have shown the validity of using this technique to quantify global, LV myocardial work efficiency non-invasively, including in a LBBB context.[2,4,5] However, the prognostic implications of global, LV myocardial work efficiency in heart failure patients undergoing CRT have not been explored. We investigated the prognostic implication of the global, LV myocardial work efficiency measured before CRT implantation.

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METHODS

Study population and definition of clinical measures

From an ongoing registry of heart failure patients treated with CRT,[6] those with class I recommendations for CRT (sinus rhythm and QRS duration ≥130 ms with LBBB morphology, LV ejection fraction (EF) ≤35% and New York Heart Association (NYHA) class II, III and ambulatory IV symptoms, despite adequate medical treatment),[3] and simultaneous, non-invasive measurement of blood pressure with brachial artery sphygmomanometry during echocardiography were selected. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Ischemic heart failure etiology was defined as the presence of significant coronary artery disease. The NYHA functional class was assessed in all patients, and a clinical response to CRT was subsequently defined as an improvement of ≥1 NYHA class at 6-month follow-up.[7] Quality of life was evaluated with the Minnesota Living with Heart Failure Questionnaire, and if the patient's condition allowed, a 6-minute walk test was also conducted.[8,9] Renal function was characterized by the estimated glomerular filtration rate (eGFR), according to the Modification of Diet in Renal Disease (MDRD) study equation.[10]

Conventional analysis of echocardiographic data

All patients underwent transthoracic echocardiography in the left lateral decubitus position with a commercially available echocardiography system (VIVID 7 or E9, General Electric Vingmed Ultrasound, Milwaukee, USA). Echocardiographic data were acquired with either 3.5 MHz or M5S transducers, while adjusting depth and gain settings as necessary. ECG-triggered, M-mode, 2-dimensional and Doppler data were digitally archived for off-line analysis (EchoPac 202, General Electric Vingmed Ultrasound, Milwaukee, USA). The LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and the LVEF were calculated with the Simpson's method from 2-dimensional, apical, 2- and 4-chamber views.[11]

Calculation and definition of global, LV myocardial work efficiency

The global, LV myocardial work efficiency was calculated by proprietary software (EchoPac 202, General Electric Vingmed Ultrasound, Milwaukee, USA) from speckle tracking echocardiographic strain data, as well as non-invasive blood pressure recordings. Speckle tracking analysis was used to measure longitudinal LV strain from standard apical views (long-axis, 2-chamber and 4-chamber).[12] The opening and closing time points of the aortic and mitral valves were identified from the parasternal, 2-dimensional images of the LV. Non-invasive blood pressure values were recorded with brachial artery sphygmomanometry at the time of transthoracic echocardiography. An LV pressure-strain curve was then constructed from the LV longitudinal strain data of the entire cardiac cycle, the mitral and aortic valve opening and closing times as well as non-invasive blood pressure values. Cardiac work was calculated automatically per myocardial segment by the abovementioned software by differentiation of the strain values over time to yield the segmental shortening rate, which was then multiplied by the LV instantaneous pressure. The resultant, i.e. instantaneous power, was subsequently integrated over time, providing values for LV segmental and total LV work as a time function.[2] Constructive work was defined as cardiac work performed during shortening of a myocardial segment in systole or during lengthening in isovolumic relaxation, whereas wasted work was defined as work performed by a segment during lengthening in systole, or during shortening against a closed aortic valve in isovolumic relaxation. The global, LV myocardial work efficiency was defined as the ratio of the constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments, as a percentage ((constructive work/(constructive work + wasted work)) x 100%) (Figure 1).

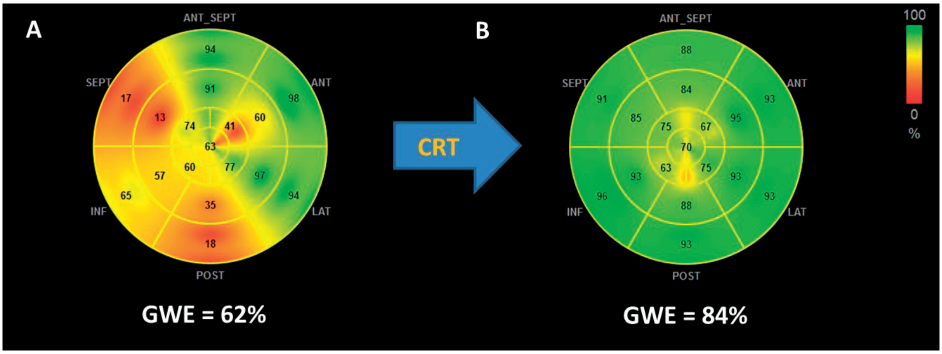

Figure 1: Change in global, left ventricular (LV) myocardial work efficiency due to effective cardiac resynchronization therapy (CRT). Parametric maps of global LV myocardial work efficiency in a patient A) before CRT and B) after 6 months of CRT. The global LV work efficiency increased from 62% to 84% after 6 months of CRT. Segmental values of LV work efficiency are expressed as percentages. CRT: cardiac resynchronization therapy, GWE: global, LV work efficiency.

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CRT implantation and follow-up

Implantation of CRT was performed according to a standard approach, i.e. insertion of the right atrial and right ventricular leads via the subclavian or cephalic veins. Before insertion of the LV lead, coronary sinus venography was performed. The LV pacing lead was then introduced into the coronary sinus through an 8 Fr guiding catheter, and positioned in a posterior or postero-lateral vein, if possible. All leads were connected to a dual-chamber, biventricular CRT device. Defibrillator functionality was included in most (99%) of the implanted devices. CRT recipients were followed up at regular intervals at the heart failure outpatient clinic, and the device was interrogated. Atrioventricular and interventricular delays were empirically set at 120-140 ms and 0 ms, respectively. CRT optimization was performed during follow-up visits at the discretion of the treating physician. A CRT response was defined by a ≥15% reduction in the LVESV after 6 months of CRT.[7] The national death registry and case records were reviewed for the occurrence of all-cause mortality during follow-up. Patients were followed up for the occurrence of the primary outcome, i.e. all-cause mortality.

Statistical analysis

Means and standard deviations were used for presenting continuous data; numbers and percentages for categorical data. Continuous variables were compared by means of Student t-tests, while χ^2 and Fisher's exact tests (as appropriate) were used for the comparison of categorical data. Values of the baseline, global, LV myocardial work efficiency were compared with a log-rank test. A Cox proportional hazards model was used to investigate the independent association between baseline, global, LV myocardial work efficiency and all-cause mortality. To show hazard change across the range of baseline global, LV myocardial work efficiency, as a continuous variable, a spline curve was fit for global, LV myocardial work efficiency vs. mortality, with overlaid confidence intervals. Subsequently, a multivariate spline model was constructed, after adjusting for the following covariates: age at implantation, gender, body mass index, ischemic etiology of heart failure, beta-blockers, diuretics, hemoglobin, renal dysfunction, LVEDV at baseline, LVEF at baseline and CRT response. In order to evaluate the incremental value of baseline, global LV myocardial work efficiency over global longitudinal strain for outcome, we performed likelihood ratio testing. SPSS for Windows, version 23.0 (SPSS, Armonk, NY, USA) and R, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) were used for performing all the analyses. All statistical tests were two-sided, and a P-value of <0.05 was considered significant.

RESULTS

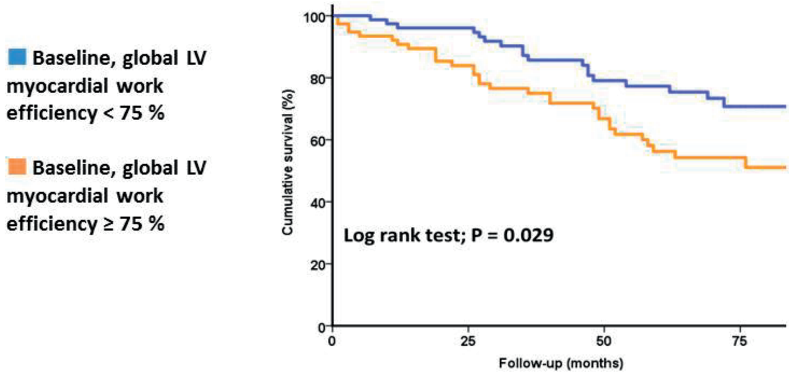
Baseline patient characteristics

In total, 153 heart failure patients treated with CRT (class I recommendation) and with echocardiographic and blood pressure data were included for analysis (mean age 66±10 years, 72% male, 48% ischemic heart disease). Strain analysis and calculation of global, LV myocardial work efficiency were feasible in all 153 (100%) patients. Baseline characteristics for the overall population are presented in Table 1. The median baseline, global, LV myocardial work efficiency was 75% (interquartile range (IQR) 66-81%). Patients were subsequently dichotomized according to the median value of baseline, global, LV myocardial work efficiency, i.e. <75% and ≥75%. CRT recipients with baseline, global, LV myocardial work efficiency <75% were more frequently female, and had larger chamber dimensions (LVEDV, LVESV) and worse systolic function (LVEF) than those with baseline, global, LV myocardial work efficiency ≥75% (Table 1).

Baseline, global, LV myocardial work efficiency and survival

In total, 47 (31%) patients died during a median follow-up of 57 months (IQR 28-76 months). Patients with less efficient mechanics at baseline (global, LV myocardial work efficiency <75%), demonstrated lower event rates than those with more efficient baseline mechanics (global, LV myocardial work efficiency ≥75%) (log-rank test, P=0.029; Figure 2). In patients with baseline, global, LV myocardial work efficiency <75%, the cumulative, all-cause mortality rates were 5, 21 and 30% at 25, 50 and 75 months follow-up, respectively. In contrast, in the group of patients with baseline, global, LV myocardial work efficiency ≥75%, the cumulative event rates were 19, 37 and 49% at the same follow-up time points.

To investigate the association between baseline, global, LV myocardial work efficiency and all-cause mortality, a Cox proportional hazards model was constructed with variables known to influence mortality of heart failure patients (Table 2). On multivariable analysis, global, LV myocardial work efficiency <75% at baseline was independently associated with better survival (hazard ratio 0.48; 95% confidence interval 0.25-0.92; P=0.027). To show hazard change across



Number of patients at risk				
Baseline, global LV myocardial work efficiency < 75 %	77	67	47	21
Baseline, global LV myocardial work efficiency ≥ 75 %	76	57	39	17

Figure 2: Kaplan-Meier curves depicting time to cumulative survival in cardiac resynchronization (CRT) recipients. Data are shown according to those with baseline, global, left ventricular (LV) myocardial work efficiency <75% and ≥75%. LV: left ventricular.

Table 1: Baseline patient characteristics.

	Overall population (n=153)	Global, LV myocardial work efficiency <75% (n=77)	Global, LV myocardial work efficiency ≥75% (n=76)	P-value
Age (years)	65.5±10.2	64.0±9.9	66.9±10.3	0.081
Male gender, n (%)	110 (71.9)	48 (62.3)	62 (81.6)	0.008
Ischemic etiology, n (%)	74 (48.4)	33 (42.9)	41 (53.9)	0.170
Heart rhythm at baseline, n (%)				
- Sinus rhythm	139 (90.8)	72 (93.5)	67 (88.2)	0.400
- Paced rhythm	14 (9.2)	5 (6.5)	9 (11.8)	0.251
NYHA class, n (%)				
- I	0 (0.0)	0 (0.0)	0 (0.0)	-
- II	48 (31.4)	22 (26.8)	26 (34.2)	0.489
- III	90 (58.8)	47 (61.0)	43 (56.6)	0.575
- IV	15 (9.8)	8 (10.4)	7 (9.2)	0.806
6 MWT (m)	344.7±114.7	371.3±111.3	316.7±112.4	0.011
QoL score	30.2±19.4	27.8±17.8	33.0±20.9	0.135
Diabetes, n (%)	24 (15.7)	8 (10.4)	16 (21.1)	0.070
eGFR <60 ml/min/1.73 m^2, n (%)	55 (35.9)	27 (38.0)	28 (40.0)	0.810
LVEF (%)	24.9±6.9	22.4±6.9	27.5±5.8	<0.001
LVEDV (ml)	216.1±78.5	232.3±81.8	199.8±71.8	0.010
LVESV (ml)	164.2±67.2	182.2±71.8	146.0±57.1	<0.001
Global, LV myocardial work efficiency (%)	74.6 (IQR 66.2-81.4)	66.3 (IQR 61.1-70.6)	81.4 (IQR 77.5-85.3)	<0.001*

Values are mean ± standard deviation, unless otherwise specified. eGFR: estimated glomerular filtration rate, IQR: interquartile range, LV: left ventricular, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, 6 MWT: 6-minute walk test, NYHA: New York Heart Association, QoL: quality of life, *per definition.

Table 2: Uni- and multivariable Cox proportional hazards models for all-cause mortality.

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Baseline, global, LV myocardial work efficiency <75%	0.535	0.302-0.948	0.032	0.484	0.254-0.922	0.027
Age at implant (years)	1.040	1.006-1.075	0.019	1.009	0.974-1.045	0.620
Male gender	1.074	0.578-1.996	0.822	-	-	-
Body mass index (kg/m^2)	0.996	0.933-1.063	0.901	-	-	-
Ischemic etiology	1.816	1.031-3.201	0.039	1.229	0.646-2.341	0.530
Beta-blockers	0.740	0.403-1.359	0.332	-	-	-
Diuretics	1.894	0.807-4.445	0.142	-	-	-
Hemoglobin (g/dl)	0.967	0.728-1.283	0.814	-	-	-
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	3.471	1.901-6.339	<0.001	3.463	1.761-6.809	<0.001
LVEDV at baseline	0.999	0.995-1.003	0.581	-	-	-
LVEF at baseline	0.995	0.955-1.036	0.804	-	-	-
Responder (≥15% reduction LVESV after 6 months)	0.534	0.294-0.969	0.039	0.575	0.302-1.095	0.092

CI: confidence interval, eGFR: estimated glomerular filtration rate, HR: hazard ratio, LV: left ventricular, LVEDV: left ventricular, end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular, end-systolic volume.

the range of baseline, global, LV myocardial work efficiency, as a continuous variable, a spline curve was fit for baseline, global, LV myocardial work efficiency vs. mortality. For all-cause mortality, predicted from the baseline, global, LV myocardial work efficiency, the assumption of linearity was violated (χ^2, 7.8; P=0.02). There was an increase of hazards for baseline, global, LV myocardial work efficiency between 70% and 85%. At very low, global, LV myocardial work efficiency values (<65%), there was also an increase of the hazards, giving a parabolic shape to the curve, although a lower frequency of observations in this range makes a meaningful, clinical interpretation less robust (also reflected in the wider confidence intervals at low baseline, global, LV myocardial work efficiency) (Figure 3A). When adjusted for multiple covariates, the assumption of linearity was not violated (χ^2, 3.7; P=0.16), and the curve demonstrated a similar shape to the unadjusted model for higher values, with hazards increasing for baseline, global, LV myocardial work efficiency between 70% and 85% (Figure 3B). At lower values (<65%) however, a plateau developed, although a low number of observations and wide confidence intervals again made clinical interpretation more challenging.

Incremental value of global, LV myocardial work efficiency

In order to evaluate the incremental value of global, LV myocardial work efficiency over global longitudinal strain for mortality, likelihood ratio testing was performed. The baseline model (model 1) comprised all risk factors which were included in the multivariable regression model, i.e.: age at implantation, ischemic etiology of heart failure, renal dysfunction and a response to cardiac resynchronization therapy (≥15% decrease in LV, end-systolic volume). Addition of

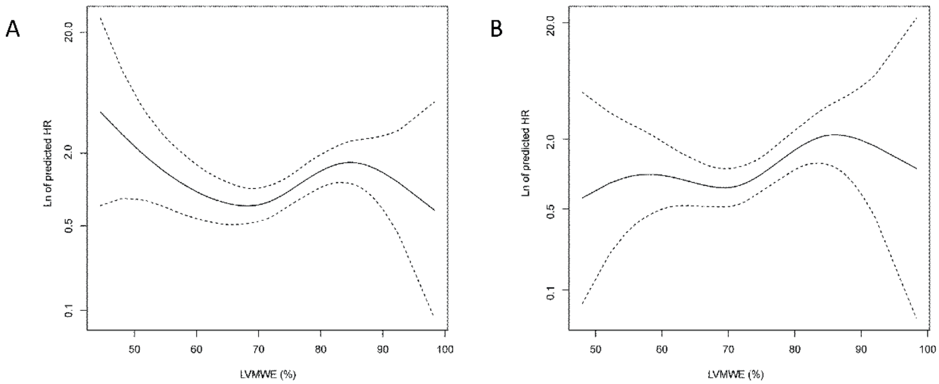


Figure 3: Spline curves for baseline, global, LV myocardial work efficiency vs. all-cause mortality. Predicted mortality across a range of baseline, global, LV myocardial work efficiency, plotted as a fitted spline model on a log-hazard scale, with overlaid confidence intervals. The unadjusted model is shown in panel A, and the adjusted model in panel B. HR: hazard ratio, Ln: logarithm, LVMWE: left ventricular, myocardial work efficiency.

baseline, global longitudinal strain to model 1, provided incremental value (P=0.029; Figure 4). A third model, which included baseline global, myocardial work efficiency, proved to be of further incremental value (P=0.002; Figure 4).

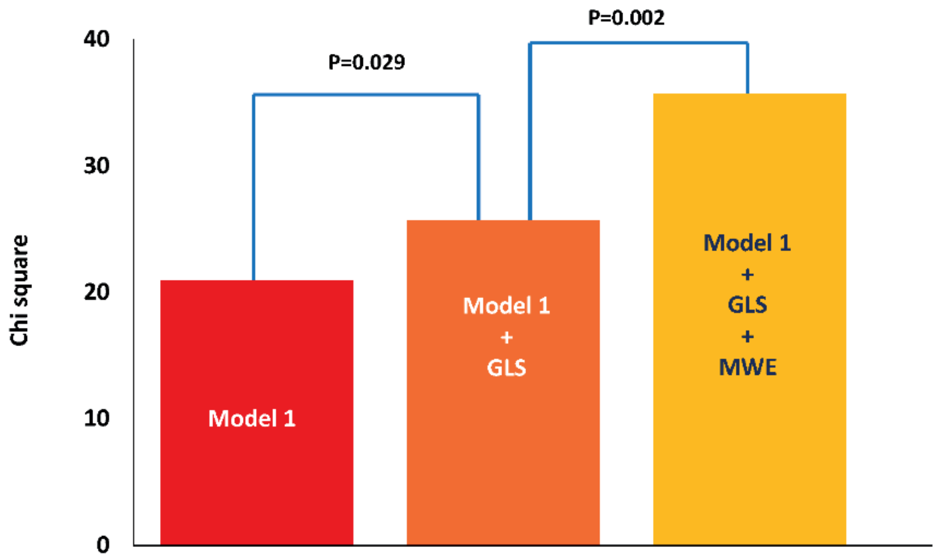


Figure 4: Likelihood ratio test. Bars represent the incremental value of global longitudinal strain and global, left ventricular myocardial work efficiency in addition to clinical risk factors (Model 1). GLS: global longitudinal strain, MWE: myocardial work efficiency.

DISCUSSION

The primary finding of the present study, is that a lower global, LV myocardial work efficiency before institution of CRT is independently associated with better long-term outcome in patients with a class I indication for CRT, according to current guidelines.

Non-invasive estimation of global, LV myocardial work efficiency

Cardiac work which is performed by an early-activated LV segment on an opposing, late-activated LV segment (elongating the late-activated segment during contraction of the early-activated segment), does not contribute to the LV stroke volume, and leads to inefficient LV function.[2] This can be quantified by the global, LV myocardial work efficiency, i.e. the ratio of the constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments, as a percentage ((constructive work/(constructive work + wasted work)) x 100%). In order to estimate the global, LV myocardial work efficiency non-invasively, wasted LV work and constructive LV work have to be measured. Since the principles of non-invasive determination apply equally well to wasted and constructive LV work (the former representing work performed by a segment during lengthening in systole, or during shortening against a closed aortic valve in isovolumic relaxation, and the latter work performed during shortening of a myocardial segment in systole or during lengthening in isovolumic relaxation), experimental studies have focused on the validity of the non-invasive estimation of cardiac work.

Echocardiography-based, non-invasive estimation of cardiac work is a novel technique, with the objective to quantify the energy efficiency of the LV.[4] In a canine validation study, a good correlation was demonstrated between invasive and non-invasive LV pressure-strain loops (r=0.96).[4] In the same study, LV work was then calculated non-invasively in humans, and compared to regional, myocardial glucose metabolism (visualized with positron emission tomography (PET)).[4] A very robust correlation was found between the non-invasive LV work and the regional, myocardial glucose metabolism (r=0.81).[4] Further evidence for the validity of the non-invasive estimation of LV work has been provided in a murine model, which indicated a strong correlation between myocardial work (non-invasively estimated with magnetic resonance imaging) and the influx rate constant of 18-fluoro-deoxyglucose (as a marker of the rate of myocardial glucose metabolism) on PET (r=0.75).[5] Since LV work can be reliably estimated non-invasively, the global, LV myocardial work efficiency can be calculated from wasted and constructive LV work. This is achieved using echocardiography and sphygmomanometric blood pressure recordings. Since electrical conduction disturbances – specifically LV dyssynchrony – influence the global, LV myocardial work efficiency, this technique can be applied to investigate the effects of CRT on myocardial energetics.

Global, LV myocardial work efficiency before CRT: implications for outcome

A lesser global, LV myocardial work efficiency before CRT was independently associated with better long-term outcome in our study. Abnormal LV activation due to a LBBB leads to dyssynchronous LV contraction, which causes an early-activated LV segment to stretch an opposing late-activated segment and vice versa, but does not contribute to stroke volume and therefore leads to inefficient LV mechanics.[2] Both the presence of an LBBB and other baseline LV dyssynchrony measures are associated with long-term outcome in CRT.[3,13-16]

Inclusion criteria for our study comprised class I indications for CRT according to contemporary guidelines, i.e. including the presence of an LBBB.[3] Despite selection of CRT recipients on the basis of a pre-existing LBBB and QRS ≥130 ms, the degree of baseline, global, LV myocardial work efficiency was independently associated with long-term survival. This difference in outcome between CRT recipients with a greater or lesser baseline, global, LV myocardial work efficiency can therefore not be attributed to the presence of LBBB-induced dyssynchrony alone. Improvement of function in areas of poorly contractile but viable myocardium by CRT, will increase the amount of constructive work performed by the LV. This so-called recruitment of contractile reserve in CRT candidates has been demonstrated with dobutamine stress-echocardiography, and it is associated with both the acute and long-term remodeling response to CRT, as well as better event-free survival.[17-21] Since global, LV constructive work correlates with myocardial metabolic activity on PET, it can be considered an indication of contractile reserve in CRT recipients.[4,20] Since the global, LV myocardial work efficiency is calculated from wasted and constructive LV work, it will improve with recruitment of contractile reserve. It therefore seems likely that, in our study patients, a difference in the contractile reserve is reflected in the baseline global, LV myocardial work efficiency, which is subsequently recruited, thereby increasing the global, LV myocardial work efficiency. Since the activation of contractile reserve in LV segments after CRT is associated with a better outcome, it is not surprising that the baseline, global, LV myocardial work efficiency is also associated with outcome. The trend towards a higher risk at very low values of global, LV myocardial work efficiency seen on both the unadjusted and adjusted spline curves (Figure 3), suggests that there may be a lower limit of contractile reserve, below which the myocardial contractile reserve is exhausted.

Furthermore, the incremental value of global, LV myocardial work efficiency over global longitudinal strain (in addition to clinical risk factors) for survival, lends additional support to the role of global, LV myocardial work efficiency as a useful imaging parameter in CRT.

Further studies, in larger populations, will be required to determine the value of measuring global, LV myocardial work efficiency before the implantation of CRT, especially with regard to selection of CRT candidates and in predicting long-term outcome. Global, LV myocardial work efficiency will be included as a parameter in the EuroCRT study, which is designed to prospectively evaluate multimodality imaging in the evaluation of various long-term outcome parameters of heart failure patients treated with CRT.[22]

Study limitations

This study is subject to the limitations of a retrospective, single-center study. Since the calculation of global, LV myocardial work efficiency is dependent on speckle tracking strain echocardiography, the results are not vendor-independent.

CONCLUSIONS

Global, LV myocardial work efficiency can be derived non-invasively from speckle tracking strain echocardiography data and sphygmomanometric blood pressure recordings. A lower global, LV myocardial work efficiency before CRT, is independently associated with better long-term outcome in heart failure patients with a class I indication for CRT, according to current guidelines. Larger studies are required to confirm the usefulness of non-invasive measurement of global, LV myocardial work efficiency in predicting CRT response, as well as in the prediction of long-term outcome after CRT.

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