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Clinical Significance of Global Wasted Work in patients with Heart Failure receiving Cardiac Resynchronization Therapy

Clemence Riolet^{1*} MD, Aymeric Menet^{1*} MD PhD, Amandine Mailliet¹ RN, Camille Binda¹ MD, Alexandre Altes¹ MD, Ludovic Appert¹ MD, Anne Laure Castel¹ MD, François Delelis¹ MD, Guillaume Viart¹ MD, Yves Guyomar¹ MD, Caroline Le Goffic¹ MD, Marie Decroocq¹ MD, Pierre-Vladimir Ennezat² MD PhD, Pierre Graux¹ MD, Christophe Tribouilloy^{3,4} MD, Sylvestre Marechaux^{1,4**} MD PhD

¹ *Université Lille Nord de France, GCS-Groupement des Hôpitaux de l'Institut Catholique de Lille, Laboratoire d'échocardiographie, service de cardiologie Nord, Centre des Valvulopathies, Faculté de Médecine et de Maïeutique, Université Catholique de Lille, Lille, France*

² *Centre Hospitalier Universitaire de Grenoble, Service de cardiologie, Grenoble, France*

³ *EA 7517 MP3CV Jules Verne University of Picardie Amiens France*

⁴ *Centre Hospitalier Universitaire d'Amiens, Amiens, France*

Short title: myocardial wasted work in CRT

**: these authors contributed equally to the preparation of the manuscript*

****** Corresponding author. Cardiology department, GCS- Groupement des Hôpitaux de l'Institut Catholique de Lille, Faculté libre de médecine / Université Catholique de Lille, Rue du Grand But, 59160 Lomme, France. Tel: +33 3 20 22 50 57. Fax: +33 3 20 22 38 59

E-mail address: Marechaux.Sylvestre@ghicl.net (S. Maréchaux).

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Abstract

Background- The relationship between myocardial work assessment using pressure-strain loops by echocardiography prior to cardiac resynchronization therapy (CRT) and response to CRT has been recently revealed. Among myocardial work parameters, the impact of left ventricular (LV) myocardial global wasted work (GWW) on response to CRT and outcome following CRT has been seldom studied. Hence, we evaluated here the relationship between preprocedural GWW and outcome in a large prospective cohort of patients with heart failure and reduced ejection fraction (HFrEF) receiving CRT.

Methods-The study included 249 HF patients. Myocardial work indices including GWW were calculated by speckle tracking strain two-dimensional echocardiography using pressure-strain loops. Endpoints of the study were 1) response to CRT defined as LV reverse remodeling and/or absence of hospitalization for HF 2) All-cause death during follow up.

Results-Median follow-up was 48 months (interquartile range 43-54). Median preoperative GWW was 281 (184-388) mmHg%. Preoperative GWW was associated with CRT response (Area Under the Curve 0.74, $p < 0.0001$), and a 200 mmHg% threshold discriminated CRT non-responders from responders with a 85% specificity and a 50% sensitivity, even after adjustment for known predictors of CRT response (adjusted OR 4.03(1.91-8.68), $P < 0.001$). After adjustment for established predictors of outcome in HFrEF patients receiving CRT, $GWW < 200$ mmHg% remained associated with a relative increased risk of all-cause death compared with $GWW \geq 200$ mmHg% (adjusted HR, 2.0; 95%CI, 1.1–3.9; $p = 0.0245$). Adding GWW to a baseline model including known predictors of outcome in CRT resulted in an improvement of this model (chi square to improve 4.85, $p = 0.028$). The relationship between GWW and CRT response and outcome was stronger in terms of size effect and statistical significance than for other myocardial work indices.

Conclusions-A low preoperative GWW (<200 mmHg%) is associated with absence of CRT response in CRT candidates and with a relative increased risk of all-cause death. GWW appears to be a promising parameter to improve the selection for CRT of HFrEF patients.

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure (HF) and reduced ejection fraction (HFrEF), impaired left ventricular (LV) function and increased QRS duration.[1] However risk stratification remains key in the management of HF patients as 30% fail to improve and may even deteriorate after CRT.[2] The identification of predictors of poor outcome following CRT is therefore of paramount importance. Despite initial disappointing results, recent studies have suggested that echocardiography may be useful to identify HFrEF patients in whom CRT will be efficient in terms of LV reverse remodeling and improved outcome.[3] Specifically, echocardiographic characterization of the mechanical consequences of an electrical activation delay due to increased QRS duration and conduction abnormalities has recently gained attention.[4, 5] Indeed, in patients with left bundle branch block (LBBB), early specific motion of the inter-ventricular septum, i.e. septal flash (SF), stretches the inactivated LV lateral wall.[6, 7] LV lateral wall activation is delayed owing to LV conduction delay, thereby resulting in delayed contraction of the stretched LV lateral wall with a late post-systolic peak. This results in the characteristic clockwise motion of the LV apex called apical rocking.[8] This delayed LV lateral wall contraction further results in septal stretching. Identification of SF and apical rocking have been positively associated with LV reverse remodeling and better outcome following CRT.[9] The relevance of these qualitative indices remains however limited, as their identification is highly dependent on the echocardiographer's experience. In addition, most of these indices integrate the LV activation delay but do not integrate the impact of residual myocardial contractility, which is prerequisite for the improvement in LV function following CRT. The amount of myocardial work that can be easily

determined with high intra- and inter-observer reproducibility using speckle tracking strain echocardiography by pressure-strain loops (PSLs) has gained attention in various clinical settings.[10-13] While previous studies have reported the relationship between myocardial work indices including Global Wasted Work (GWW) and CRT response, [14-16], the link between GWW and outcome has been seldom studied and divergent results have been noted.[15, 17] Therefore, we aimed in the present study to evaluate the relationship between myocardial work indices obtained by PSLs and particularly GWW, response to CRT and long-term mortality during follow up in a large cohort of patients receiving CRT in clinical practice.

Material and methods

Study population and clinical data

The population consisted of ambulatory HF_rEF patients referred to Groupement des Hôpitaux de l'Institut Catholique de Lille (Université Catholique de Lille), Hôpital Saint Philibert, Lomme, France, for CRT device implantation between 2010 and 2017. This study was a retrospective analysis of a prospective registry.[18, 19]

CRT was indicated in patients with HF_rEF and increased QRS duration. HF_rEF was defined as the presence of HF (New York Heart Association (NYHA) class II, III, or ambulatory IV) despite optimal medical treatment and LV ejection fraction (LVEF) $\leq 35\%$. Increased QRS duration was defined as QRS duration 120 ms or more in patients with LBBB morphology or QRS duration 150 ms or more in patients with non-LBBB morphology.[20] Exclusion criteria were any one of the following characteristics: recent (< 3 months) acute coronary syndrome or coronary revascularization; primary mitral or aortic valve disease \geq moderate; atrial fibrillation with rapid ventricular response according to current clinical practice guidelines; impossibility to perform speckle tracking strain echocardiography for GWW assessment. Secondary mitral regurgitation

from any grade of severity was not an exclusion criterion. Patients in atrial fibrillation with regular, controlled heart rates allowing speckle tracking assessment were also included. All patients received maximally tolerated doses of HF medications.

Epidemiological, clinical and biological characteristics collected in the present study are detailed in **Table 1**. The etiology of LV dysfunction was deemed to be ischemic if the patient had a history of previous myocardial infarction or significant coronary artery disease on coronary angiography (>50% stenosis of an epicardial vessel).

The study was approved by the Lille Catholic University ethics committee for non-interventional research. Informed consent was obtained at the time of enrollment from all patients. Registered clinical trial number is **NCT02986633**.

Echocardiography

Echocardiograms were performed by experienced echocardiographers using a Vivid E9 or a E95 commercial ultrasound scanner (General Electric Healthcare, Horten, Norway) with a phased-array transducer (M5S-D) on the day before CRT implantation (TTE 1), before hospital discharge (TTE 2) and at 9 months follow-up for the assessment of response to CRT (TTE 3). Non-invasive blood pressure values were recorded with brachial artery sphygmomanometry at the time of transthoracic echocardiography.

Standard echocardiographic measurements were performed according to the ASE (American Society of Echocardiography) / EACVI (European Association for Cardiovascular Imaging) guidelines.[21] LV electromechanical dyssynchrony was identified by searching for either septal flash (SF) on short- or long-axis parasternal views or LV apical rocking in apical 4-chamber view.[3] Apical chamber views recorded at a frame rate between 55 and 90 fps (65±10 fps) were used for strain analysis. Longitudinal 2D-speckle-tracking strain curves were analyzed off-line on a dedicated workstation (EchoPAC PC, General Electric Healthcare, Velizy, France).

Longitudinal strain values were computed after determining aortic valve opening and closure onset using Doppler recordings. Automatic tracking of the endocardial contour on an end-systolic frame was carefully verified and the region of interest was manually corrected to ensure optimal tracking and to cover the entire thickness of the LV myocardium. LV GLS was the average of segmental peak systolic longitudinal strains occurring before aortic valve closure. Segments which displayed akinesis or dyskinesis in combination with a disproportionate local wall thinning and hyperreflectivity in comparison with adjacent contractile segments were scored as “scarred.”[22] LV myocardial scar was considered significant if at least 3 myocardial segments were scored as scarred.

Global wasted work assessment (Figure 1)

An LV pressure-strain curve was then constructed from the LV longitudinal strain data of the entire cardiac cycle and the mitral and aortic valve opening and closing times as well as the non-invasive blood pressure values.[23] Myocardial work was calculated automatically per myocardial segment by the EchoPAC PC software (General Electric Healthcare, Velizy) by differentiation of the strain values over time to yield the segmental shortening rate, which was then multiplied by an approximation of the LV instantaneous pressure. The resultant, i.e. instantaneous power, was subsequently integrated over time, providing values for LV segmental and total myocardial work as a time function. (4) Myocardial work was calculated from mitral valve closure until mitral valve opening (mechanical systole including isovolumic relaxation (IVR)). The work performed by the myocardium during segmental lengthening, which does not promote LV relaxation, is considered wasted work, whereas the work performed by the myocardium during segmental shortening is considered segmental constructive work. By averaging segmental constructive and wasted work for each segment, global constructive work (GCW) and global wasted work (GWW) were estimated for the entire LV. The Global Work Efficiency (GWE) 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%]. The difference in GWW values between TTE1 and TTE2 (Δ GWW) was also calculated.

Intraobserver reproducibility of GWW was determined using data produced by one investigator (C.R.) who performed a second analysis of stored echocardiograms from 15 randomly selected patients. This second analysis was performed three months after the first analysis. A second investigator (S.M.) independently repeated the analyses to test GWW interobserver variability. Investigators were blinded to outcome data.

CRT device implantation

Boston Scientific (Natick, MA), Medtronic (Minneapolis, MN), St. Jude Medical (St Paul, MN), Sorin (Milan, Italy), and Biotronik (Berlin, Germany) CRT devices were implanted by electrophysiologists targeting a basal lateral, anterolateral, or posterolateral coronary sinus vein for LV lead positioning. Interventricular timing was set at zero. A short-sensed atrioventricular delay (between 80 and 100 ms) and a paced delay (130 ms) were programmed to promote biventricular pacing. Attention was paid before hospital discharge to verify the absence of fusion or pseudo-fusion beats on the ECG and continuous monitoring.

Outcome

Response to CRT was defined as a relative reduction in LV end-systolic volume from baseline to 9 months follow up $\geq 15\%$ and/or absence of hospitalization for heart failure during follow up.[18, 24, 25] During follow-up, patients were monitored by their primary care physicians. Events were recorded by clinical interviews and/or by phone calls to physicians, patients, and (if necessary) next of kin. The primary study endpoint was all-cause mortality. Cardiovascular

mortality was considered if death was related to HF, myocardial infarction, arrhythmia, or sudden death.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation (SD) or median (interquartile range [IQR]) and categorical variables as absolute numbers and percentages. The Pearson χ^2 statistic or Fisher's exact test was used to examine the associations between 2 groups and baseline categorical variables. Individual differences were compared using Mann-Whitney U tests and Student's T tests for normally distributed data. Variability was expressed with the intraclass correlation coefficient (ICC). The correlations between two continuous variables were assessed using Pearson's coefficient. All ICC estimates and their 95% confidence intervals (95% CIs) were calculated based on a single rater/measurement, absolute-agreement, two-way fixed-effects model. Intra- and interobserver variabilities of GWW were also evaluated by the mean of the coefficient of variation for each GWW measure.

ROC curves were built to evaluate the value of GWW to discriminate CRT responders and non-responders. The ROCR package in R was used to evaluate and graphically display the accuracy of each GWW cutoff. The accuracy is defined as the number of accurate predictions for a given cutoff-value divided by the total number of individuals. In the present case, it corresponds to the number of patients accurately predicted as responders or non-responders divided by the total number of patients. The R software calculates the accuracy for each cutoff value and display them graphically. Comparison between ROC curves were performed using the Hanley & McNeil method. Multivariate logistic regression analysis models were built to investigate the relationship between the optimal GWW cutoff obtained with ROC analysis and response to CRT. Model building techniques were not used and covariates entered in the model were considered as classically associated with response to CRT on an epidemiological basis.[26] These covariates

included: sex, coronary artery disease (CAD), QRS width, LBBB, history of atrial fibrillation, amount of myocardial scar, and flash and/or apical rocking. To avoid collinearity, a tolerance measure (equal to the inverse of the variance inflation factor) greater than 0.7 was necessary for each variable entered in the multivariable model. To assess the improvement of the basal model build with established predictors of response to CRT when adding preprocedural GWW, we evaluated changes in the Bayesian Information Criteria (BIC) of the combined model over the baseline model and we used the Likelihood ratio test statistic.

Event rates \pm standard errors of the overall population and of two groups or more were estimated according to the Kaplan-Meier method and compared using two-sided log-rank tests. Univariate and multivariate analyses of time to events were performed using Cox proportional-hazards models. Covariates in multivariate Cox models were age, QRS width, presence of LBBB, NYHA functional class, coronary artery disease, serum creatinine level, LVEF, GLS and presence of electromechanical dyssynchrony (SF and/or apical rocking). The proportional-hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. All hazard ratios (HRs) for continuous variables including GWW were rescaled using the within-study SDs in Cox models. For continuous variables, the assumption of linearity was assessed by plotting residuals against independent variables. Penalized smoothing splines (P-splines) were used to illustrate mortality risk-GWW associations (GWW as a continuous variable) during follow-up and to evaluate optimal threshold. To assess the improvement of a baseline Cox multivariate model build with classical predictors of outcome in CRT when adding preprocedural GWW, we evaluated the increase of the chi-square value of the combined model over the baseline model. The increased discriminative value of GWW was also investigated by estimating the Harrell C statistic for models with and without GWW. To allow a comparison between C statistics, a total of 999 bootstrap samples of the patients in our study population were generated using the library (boot) in R, and the difference in Harrell C statistics between the

models with and without GWW was computed for each of the 999 samples. We hence obtained the 95% bootstrap CIs of the 999 estimates, for which the lower and upper bounds were the 2.5th and 97.5th percentiles of the resampling distribution, respectively.

We aimed also at identifying if there was a difference in the prognostic value of GWW in patients with and without an ischemic etiology of LV dysfunction. Hence, a first order interaction term (between GWW and categories of subgroups, corresponding to the product of these 2 variables) was systematically included in a Cox model including GWW and the ischemic etiology. A significant interaction was considered in case of a P-value for the interaction variable < 0.05 .

All p values were the results of two-tailed tests and were considered significant when < 0.05 .

Data were analyzed with R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria), and MedCalc version 12.5.0 (MedCalc Software, Mariakerke, Belgium).

Results

Baseline patient characteristics (Table 1)

The study population consisted of 249 HF patients who underwent CRT. Mean age was 72 ± 11 years and 159 (64%) patients were men (Table 1). Obstructive coronary artery disease was found in 96 patients (39%). Seventy patients (28%) had a history of AF. Among these 70 patients, 34 had paroxysmal AF and were in sinus rhythm at the time of the index echocardiogram. The remaining 36 patients had regular atrial fibrillation and controlled heart rates allowing speckle tracking assessment. The electrocardiogram showed LBBB in 177 patients (71%). Median QRS width was 160 [150;180] ms. The majority of patients had a QRS width > 130 ms (94%), only 14 patients (6%) had a QRS width between 120 and 130 ms. Mean LVEF was $26 \pm 5\%$. 202 patients (81%) received CRT-D while 47 (19%) received CRT-P.

Relationship between myocardial work indices and response to CRT

CRT response was assessed in 91% of the study population (227 patients) and 149 patients were CRT responders (66%). The area under the ROC curve (AUC) of GWW, septal WW, lateral WW, GCW and GWE for the discrimination between CRT responders and non-responders are displayed in **table 1**. The AUC of GWW was 0.74 (0.68-0.80), $P < 0.0001$, indicating an acceptable predictive value. As shown in **table 1**, this AUC was significantly higher for GWW than for GCW and GWE (both $p < 0.05$), while the AUC was similar between GWW, lateral and septal WW ($p = 0.09$ and $p = 0.30$ respectively). The accuracy of each GWW cutoff is graphically displayed in **Figure 2**. An optimal cutoff value of 174 mmHg% was found (accuracy 0.74), a value close to 200 mmHg% (accuracy 0.73), which is easier to handle in clinical practice. 126 patients with $GWW \geq 200$ mmHg% were responders while 39 were not. 39 patients with $GWW < 200$ mmHg% were non-responders while 23 were responders. Therefore, 76% of patients with $GWW \geq 200$ mmHg% were CRT responders while only 37 % of patients with $GWW < 200$ were ($P < 0.001$). Hence, a GWW 200 mmHg% threshold discriminated CRT non-responders from responders with a 85% specificity and a 50% sensitivity. In comparison, 140 patients with SF and/or apical rocking were CRT responders while 52 were CRT non-responders. 26 patients without SF and/or apical rocking were CRT non-responders while 9 were responders. Hence, absence of SF and/or apical rocking discriminated CRT non-responders from responders with a 94% specificity but with a very low sensitivity at 33%. By multivariate logistic regression, $GWW < 200$ mmHg% (OR 4.03 (1.91-8.68), $P < 0.001$), lack of LBBB on the EKG (OR 2.43 (1.08-5.55), $P = 0.0326$), and presence of significant LV myocardial scar (OR 4.22 (1.54-12.07), $P = 0.006$) were independently associated with non-response to CRT, while presence of SF and/or apical rocking was not ($p = 0.064$). Adding $GWW < 200$ mmHg% to the multivariable model including sex, CAD, QRS duration, LBBB, atrial fibrillation, myocardial scar, and SF and/or apical rocking improved the performance of the multivariable model (decrease in BIC from 287 to 279, $P = 0.0003$).

Characteristics of patients according to GWW \geq or $<$ 200 mmHg%

Median preprocedural GWW was 281 [184-388] mmHg%. The characteristics of the study population according to GWW \geq or $<$ 200 mmHg% are detailed in **table 2**. Briefly, patients with GWW $<$ 200 mmHg% were more frequently male, had more frequently severe heart failure symptoms than those with GWW \geq 200 mmHg. They had also lower systolic blood pressure, narrower QRS, had less frequently a LBBB, and had higher plasma BNP levels than those with GWW \geq 200 mmHg. In addition, LVEF was lower while LV volumes were more enlarged in patients with GWW $<$ 200 mmHg% compared with those with GWW \geq 200 mmHg%. They had also less frequently LV electromechanical dyssynchrony as indicated by a lower frequency of SF/apical rocking.

Relationship between GWW and outcome

During a median 48-month [IQR 43-54] follow-up, there were 72 deaths (29%). As depicted in **table 3**, among MW parameters, the relationship between GWW and mortality was the strongest in terms of size effect and statistical significance. The shape of the GWW / mortality risk relationship is depicted in **Figure 3**. A rounded 200 mmHg% threshold, a cutoff value easy to handle in clinical practice, was therefore identified from this spline curve. As depicted in **figure 4A**, 3-year mortality-free survival was 62 (50-75%) for GWW $<$ 200 mmHg% and 83 (77-89%) in those with GWW \geq 200 mmHg% ($p=0.006$). After adjustment, GWW $<$ 200 mmHg% remained associated with a relative increased risk of death compared with GWW \geq 200 mmHg% (adjusted HR, 2.04; 95%CI, 1.10–3.84; $p = 0.0245$; **Table 3, Figure 4B**). GWW addition improved the baseline model multivariate model built with classical predictors of outcome in CRT (chi square to improve 4.85, $P=0.028$). No significant interaction was found between GWW $<$ 200 mmHg%, ischemic etiology and mortality ($P=0.11$). Presence of significant LV

myocardial scar assessed by echocardiography was associated with mortality risk (HR: 2.44 (1.38-4.33), $p=0.0023$). However, further adjustment for myocardial scar (sensitivity analysis) did not alter the relationship between $GWW < 200\%$ and mortality (adjusted HR 2.17; 95%CI 1.14-4.00, $p=0.018$). In **table 3** is also depicted the relationship between myocardial work indices and cardiovascular mortality. As for overall mortality, among myocardial work parameters, GWW had the strongest relationship with cardiovascular mortality. No multivariate analysis was however performed for this endpoint owing to the limited number of events ($n=42$), to avoid statistical overfitting.

Relationship between GWW, Δ GWW and all-cause death

Preprocedural GWW strongly correlated with immediate changes in GWW after CRT ($r=0.82$, $P<0.0001$, **Figure 5**). Among the 171 patients with $GWW \geq 200$ mmHg%, 147 (86%) experienced a decrease in GWW immediately after CRT. In contrast, among the 65 patients with $GWW < 200$ mmHg%, 33 (51%) experienced an increase in GWW immediately after CRT ($p<0.0001$). While GWW as a continuous variable was independently associated with death risk (**Table 2**), Δ GWW was not associated with death in multivariate analysis (adjusted HR 0.81; 95%CI 0.60-1.09, $P=0.164$).

Reproducibility

Both intra- and interobserver variabilities for GWW measurement were good as indicated by their intraclass correlation coefficients at 0.98 [95%CI 0.94-0.99] and 0.97 [0.92-0.99] respectively. Consistently, both intra- and interobserver coefficients of variation were low at 8.8 and 9.7% respectively.

Discussion

The present data indicate that 1) a low GWW is strongly associated with a poor outcome and absence of response to CRT in a cohort of HF patients receiving CRT in clinical practice 2) GWW provides additional prognostic information over established predictors of outcome 3) while immediate changes in GWW are strongly correlated with baseline GWW (i.e. the higher the baseline GWW, the greater the decrease in GWW following CRT), immediate changes in GWW do not provide meaningful prognostic information as compared with preprocedural GWW.

Risk stratification in HFrEF for refining death risk is importantly needed for the care of patients. The seminal CARE-HF randomized controlled trial demonstrated impressive benefits of CRT in HFrEF patients having prolonged QRS duration.[27] During a mean follow-up of 29 months, all-cause death was reduced by 36% and unplanned hospitalization for HF worsening by more than 50%. Substantial reverse LV remodeling is often produced by resynchronizing disorganized stretched walls. However, around 30% of HF patients may still not respond to the CRT.[1] Finding new simple indices that may help to refine CRT indications is therefore an important field of research.[3, 28, 29]

Non-invasive measurement of myocardial and wasted work

The amount of myocardial work can be non-invasively obtained by quantifying the area of segmental pressure-strain loops. This non-invasive measure has shown a good correlation with invasive work obtained using micromanometer catheters and sonomicrometry,[23]. In contrast to classical dyssynchrony indices, pressure strain loops estimate non-invasively LV performance and correlate with the residual myocardial metabolic activity assessed by FDG positron emission tomography in patients awaiting CRT [23, 30] Myocardial work is easily determined with high intra- and inter-observer reproducibility using speckle tracking strain echocardiography by fully

automized pressure-strain loops.[10, 23] Determining myocardial work requires the same prerequisites as for GLS, i.e. acquisition of the three apical views (4-, 2- and 3- chamber views) with an adequate frame rate and concomitant non-invasive blood pressure measurement. Russell et al first described the non-invasive assessment of myocardial work.[23] Indeed, LV pressure (LVP) curve can be reasonably estimated by deforming a standard pressure curve pattern according to the cardiac time intervals of the heart and brachial blood pressure. Hence, regional LV PSLs could be obtained from the estimated LVP in combination with regional LV deformation assessed by speckle-tracking echocardiography. The segmental WW corresponds to the work performed by the myocardium during segmental lengthening. GWW was obtained by averaging segmental WW curves for the entire LV. Importantly, Russell and colleagues reported that patients with cardiomyopathy and LBBB have increased GWW compared with cardiomyopathy patients without LBBB and healthy controls.[30] Indeed, GWW gives an overall quantitative assessment of wasted energy because early and late stretching events may be qualitatively identified only in a variable amount of segments or walls. Interestingly, we observed here that in patients with HFrEF and an activation delay as indicated by LBBB and/or increased QRS duration, the amount of wasted energy is variable, as indicated by the GWW distribution in this population. Indeed, multiple intricate factors influence GWW. First, LV geometry and dilation strongly influence myocardial work estimation.[31] By definition, work is the product of force times length and corresponds to the area of the pressure volume loop; given that longitudinal shortening describes most of LV volume changes, LV myocardial work can be approximated using pressure and strain curves. Importantly, myocardial work highly depends from LV wall stress. LV wall stress increases with LV dilation, but is not taken into account when studying pressure-strain loops. Hence, of 2 ventricles with different sizes, systolic wall stress would be higher in the dilated LV compared with the non-dilated LV, thereby potentially resulting in an underestimation of LV myocardial work. The assessment of the LV segmental

radius of curvature and wall thickness has been previously used to derive non-invasively wall stress in order to overcome this important limitation but remains cumbersome for clinical daily practice.[32] Advances in 3D echocardiography may help to improve the non-invasive assessment of wall stress in daily practice. In addition, the arterial cuff pressure used at the time of echocardiography is only an estimate of LV systolic cavity pressure and does not take into account LV diastolic pressure and pressure augmentation by reflected waves; validation studies have nonetheless demonstrated its accuracy for calculation of myocardial work by echocardiography.[33] Dyssynchronous contractions and post-systolic shortening, both conditions encountered in myocardial ischemia, may contribute to a less efficient ejection and an increased WW.[34] While Chan and colleagues found that patients with non-ischemic cardiomyopathy had higher GWW values than those with ischemic cardiomyopathy [35], we did not find in the present report a significant interaction between ischemic etiology, $GWW < 200$ mmHg% and outcome. However, cardiac magnetic resonance was not performed in the present study, and the assessment of myocardial scar was only by echocardiography which has important limitations. Aalen et al found that both myocardial work and septal viability by cardiac magnetic resonance predicted CRT response, with an incremental predictive value.[28]

Clinical impact of wasted work in CRT recipients

We demonstrated here that a low preprocedural GWW (< 200 mmHg%) is associated with a relative increased risk of death compared with $GWW \geq 200$ mmHg% and that $GWW < 200$ mmHg% is associated with a high probability of non-response to CRT. Such a finding is not unexpected, as low GWW represents the effect of not only minimal LV wall stretching that may result from an absence of electromechanical dyssynchrony but also from LV geometry and dilation. Lim and colleagues previously reported that the strain-delay index, an index of myocardial WW, correlates with CRT response.[36] In addition, Galli and colleagues found in reports involving 97 patients that GWW is associated with CRT response, with a lower predictive

value than GCW.[14, 16] In addition, the same authors observed an independent relationship between GCW and occurrence of cardiac death during follow up, but found no independent relationship between GWW and occurrence of cardiac death.[15] Van der Bijl and colleagues found an independent relationship between global LV wasted work ratio and mortality during follow up in 153 patients receiving CRT.[17] We observed here a strong relationship between preprocedural GWW, CRT response and mortality. Although the presence of SF and/or apical rocking was associated with CRT response as previously reported, its discriminant value was lower than GWW. In addition, SF/apical rocking did not remain significantly associated with both CRT response and mortality during follow up after adjustment. Such a finding is not unexpected, as the identification of SF/apical rocking is qualitative and may suffer from reproducibility issues in clinical practice.[9] Strikingly, among myocardial work parameters, the relationship between GWW, CRT response and mortality was the strongest; potential explanations for the apparent discrepancy between Galli's findings and those from the present study may be due to differences in sample size, event rates and study endpoints (overall versus cardiac mortality). Further larger multicenter studies are needed to elucidate the relative predictive value of myocardial work parameters. Although the role of septal motion and work is key in the pathogenesis of CRT response[29, 37], we observed that GWW and septal WW had a similar discriminative value for CRT response; therefore, we purposefully retained GWW for clinical practice as only this parameter can be semi-automatically obtained from the currently available software for measuring myocardial work parameters.

Strikingly, we observed here that immediate changes in post-CRT GWW were tightly correlated with preprocedural GWW. Indeed, CRT, by correcting the electrical activation delay, has the potential to reduce LV wall discoordination and abnormal stretching, thereby providing an explanation for the immediate impact of CRT on GWW. Consistently, while preprocedural GWW was independently associated with mortality in the present study, acute changes in GWW

were not. This finding therefore suggests that the impact of CRT on outcome is at least partially determined by the preprocedural amount of wasted energy. Effective resynchronization systematically reduces preprocedural GWW, which in turn translates into better outcome.

Limitations

The present study has limitations inherent to its observational nature. Whereas echocardiograms were prospectively collected, follow-up data were obtained retrospectively. We agree that the wide variability of myocardial work parameters may be a limitation for the application of this technique in the routine clinical setting.[38] Myocardial work can be assessed as yet only with one vendor's equipment and software (General Electric). Lastly, CRT pacing settings were commonly not changed or adjusted during the time period of the study. Indeed, a meta-analysis of 12 trials comparing AV and/or interventricular delay optimization and conventional CRT device programming found that AV and/or interventricular delay optimization had a neutral effect on clinical and echocardiographic outcomes.[39]

Conclusions

Preprocedural GWW assessed by PSLs is reproducible, and GWW low values are associated with poor long-term outcome and a lower CRT response rate in HFrEF patients receiving CRT. GWW < 200 mmHg% provides independent prognostic information over established predictors of outcome in this population of HFrEF patients. However, in the absence of randomized controlled studies, even if a majority of patients with a preprocedural GWW < 200 mmHg% seem to not derive benefit from CRT, these patients should not be excluded from CRT. Daily practice for now should rely on current practice guidelines.[1] Therefore, the results of the present study suggest that patients with low preprocedural GWW should be carefully monitored after CRT to ensure timely referral for advanced therapy (heart transplantation, left or biventricular assist devices) before their clinical condition worsens.

Disclosure of interest

The other authors declare that they have no conflicts of interest concerning this article.

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	AUC 95% CI	P-value versus Global Wasted Work
Global Wasted Work	0.74 (0.68-0.80)	...
Septal Wasted Work	0.77 (0.71-0.82)	0.30
Lateral Wasted Work	0.67 (0.60-0.73)	0.09
Global Work Efficiency	0.63 (0.57-0.70)	0.002
Global Constructive Work	0.66 (0.59-0.72)	0.039

Table 1: Area Under the ROC Curve (AUC) for myocardial work parameters for the prediction of response to CRT. CI, confidence interval.

	All N=249	GWW< 200 mmHg% N=70	GWW ≥ 200 mmHg% N=179	P-value
<i>Demographic and clinical data</i>				
Age (years)	72 ± 11	69 ± 13	72±10	0.08
Male gender, n(%)	159 (64)	56(80)	103(58%)	0.002
BMI (kg/m ²)	28 ± 14	27 ± 5	29±17	0.24
Diabetes mellitus, n(%)	75 (30)	18(26)	57(32)	0.43
Dyslipidemia, n(%)	111 (45)	29(41)	82(46)	0.60
CAD, n(%)	96 (39)	31(44)	65(36)	0.31
History of AF, n(%)	70 (28)	22(32)	48(27)	0.52
NYHA functional class III-IV n(%)	118 (47)	38(54)	80(45)	0.05
Heart rate (bpm)	72 ±14	74 ±15	72±14	0.33
SBP (mmHg)	123 ± 21	109 ± 18	129±19	<0.001
QRS width (ms)	160 [150;180]	160 [140;164]	160 [160;180]	<0.001
QRS width ≥ 150 ms, n(%)	202(81)	47(67)	155(87)	0.001
LBBB, n(%)	177 (71)	42(60)	135(75)	<0.001
Beta blockers, n(%)	224 (90)	61(87)	163(91)	0.49
ACE inhibitors/ARB, n(%)	218 (88)	60(86)	158(88)	0.7
Aldosterone antagonist, n(%)	79(32)	25(41)	51(29)	0.1
<i>Biological data</i>				
Creatinine (mg/dL)	10.7 [8.3;13.4]	11.9 [9.9;14.3]	11.4 [9.1;14.3]	0.27
BNP (pg/mL)*	337 [159;641]	636 [322;1224]	346 [144;810]	0.001
<i>Echocardiographic data</i>				
LV Ejection Fraction (%)	26 ± 5	25 ± 5	27±5	0.001
Significant LV myocardial scar, n(%)	26 (15)	7(14)	19(15)	0.98
GLS (%)	6.3±2.7	6.2±2.6	6.3±2.8	0.78
LV end-diastolic volume (mL)	236 [194;288]	264 [214;304]	220 [185;274]	0.001
LV end-systolic volume (mL)	171 [141;215]	190 [162;225]	162 [135;203]	<0.001
Septal flash or apical rocking, n(%)	210(84)	44(63)	166(93)	<0.001
GWW (mmHg%)	281 [184;388]	156 [112;173]	342 [263;433]	By design

Table 2 : Baseline characteristics of the study patients according to GWW < and ≥ 200 mmHg%; Data are expressed as mean ± SD or median (IQR); *data available in 127 patients; BMI: Body Mass Index; CAD: Coronary artery disease; AF: atrial fibrillation; NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; LBBB: left bundle branch block; RV: right ventricular; ACE: angiotensin-converting-enzyme; ARB: angiotensin receptor blocker; BNP: brain natriuretic peptide; LV: left-ventricular; GLS: Global Longitudinal Strain; GWW: global wasted work.

	All-cause mortality		Cardiovascular mortality	
	Hazard Ratio 95% CI	P-Value	Hazard Ratio 95% CI	P-Value
Global wasted work	0.66 (0.50 - 0.89)	0.00564	0.48 (0.31 - 0.75)	0.00108
Global work efficiency	1.24 (0.99 - 1.57)	0.0662	1.49 (1.09 - 2.04)	0.0131
Global constructive work	0.77 (0.59 – 1.00)	0.0514	0.74 (0.53 - 1.04)	0.087

Table 3: Relationship between myocardial work indices and mortality by Cox univariate analysis; HR, Hazard ratio; CI, confidence interval

	Univariate analysis		Multivariate analysis (model 1 without GWW)		Multivariate analysis (model 2 with GWW<200 mmHg%)	
	Crude HR (CI 95%)*	p	Adjusted HR (CI 95%)	p	Adjusted HR (CI 95%)	p
Age (per SD)	2.13 (1.58 - 2.87)	<0.001	2.04 (1.45 - 2.87)	<0.001	2.13 (1.53 - 2.96)	<0.001
Sex	1.53 (0.92 - 2.55)	0.101	1.66 (0.94 - 2.91)	0.0793	1.31 (0.72 - 2.39)	0.379
QRS width (per SD)	1.08 (0.87 - 1.34)	0.497	0.93 (0.73 - 1.17)	0.522	0.99 (0.78 - 1.27)	0.966
NYHA III-IV	2.71 (1.65 - 4.45)	<0.001	1.79 (1.05 - 3.05)	0.0322	1.77 (1.03 - 3.01)	0.0372
Coronary artery disease	2.03 (1.27 - 3.22)	0.00284	1.63 (1.00 - 2.65)	0.048	1.70 (1.05 - 2.75)	0.0317
Creatinine (per SD)	1.53 (1.33 - 1.75)	<0.001	1.4 (1.19 - 1.64)	3.41e-05	1.33 (1.13 - 1.56)	0.000453
LV ejection fraction (per SD)	0.77 (0.61 - 0.98)	0.0341	0.71 (0.53 - 0.97)	0.0284	0.77 (0.57 - 1.04)	0.0877
Left Bundle Branch Block	0.73 (0.43 - 1.21)	0.219	1.05 (0.59 - 1.87)	0.878	1.06 (0.61 - 1.87)	0.828
Global longitudinal strain (per SD)	1.07 (0.98 - 1.17)	0.139	0.99 (0.89 - 1.11)	0.917	1.00 (0.90 - 1.12)	0.944
Septal flash and/or apical rocking	0.46 (0.26 - 0.79)	0.00499	0.65 (0.35 - 1.21)	0.176	0.83 (0.44 - 1.57)	0.561
GWW (per SD)	0.66 (0.50 - 0.89)	0.00564	NA	NA	NA	NA
GWW < 200 mmHg%	0.48 (0.30 - 0.77)	0.00244	NA	NA	2.04 (1.10 - 3.84)	0.0245
BIC	NA	NA	683		682	Model 1 versus 2 P value = 0.028
Harrell C statistic	NA	NA	0.767		0.775	
C statistic difference (95% CI)	NA	NA			-0.0003; 0.0829	

Table 4: Relationship between Global Wasted Work (GWW), variables of interest and mortality during follow up. Model 1 is the model without GWW, while GWW < 200 mmHg% is added in model 2. HR, Hazard Ratio; LV, left ventricular; BIC: Bayesian Information Criterion; SD: Standard Deviation

Figure legends

Figure 1: principle of the assessment of myocardial wasted work on 2 representative segments (basal inferolateral and anterolateral) obtained in apical 4 chamber view; pressure strain loops (PSLs) are obtained from strain curves obtained by speckle tracking imaging and systolic blood pressure assessment for a basal septal segment (green curve) and for a basal lateral segment (red curve) ; Segmental work is derived from these PSLs, and the magenta portion of the curves corresponds to the wasted work. LV: left ventricle; MVO: mitral valve opening; MVC: mitral valve closure; AVC: aortic valve closure; AVO: aortic valve opening.

Figure 2: Graphical representation of the accuracy of each Global Wasted Work (GWW) value to predict response to CRT. The vertical dotted line corresponds to the 200 mmHg% threshold.

The accuracy is defined as the number of patients accurately predicted as responders or non-responders divided by the total number of patients. The 200 mmHg% cutoff value gives the highest accuracy. Increasing Global Wasted Work (GWW) values increases the likelihood of being a responder at the expense of a poor prediction of being a non-responder, hence resulting in decreased accuracy.

Figure 3: Relationship between Global Wasted Work (GWW) and mortality during follow-up.

HRs and 95% CIs are estimated in a Cox model with GWW represented as a spline function.

Figure 4: Kaplan Meier estimates of survival free from death (A), according to Global Wasted

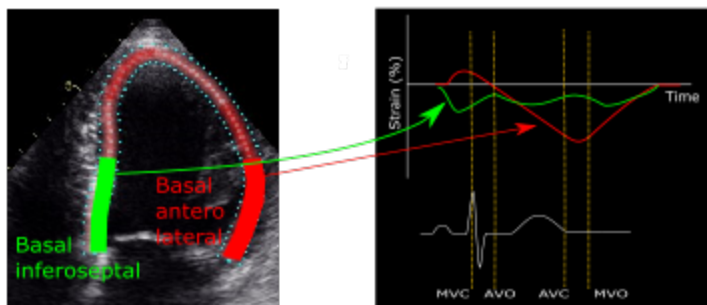
Work (GWW) $<$ and \geq 200 mmHg% and adjusted survival free from death (B), according to

GWW $<$ and \geq 200 mmHg%. a = adjusted. No: number.

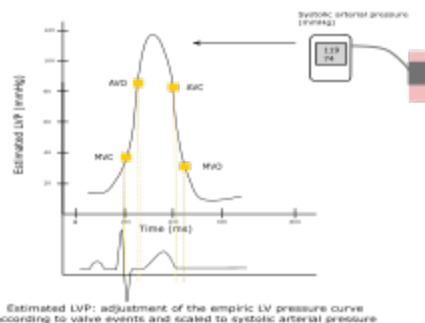
Figure 5: Relationship between preoperative Global Wasted Work (GWW) and immediate

changes in GWW (Δ GWW, %). The line is the regression line.

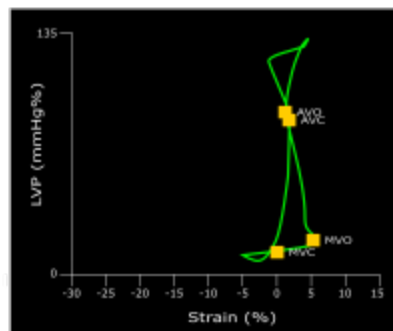
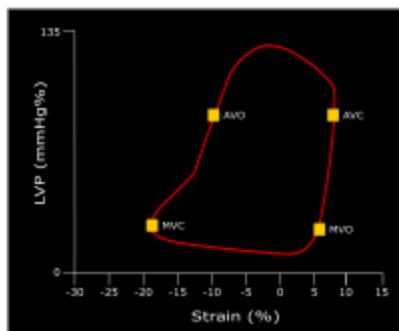
Segmental strain curves



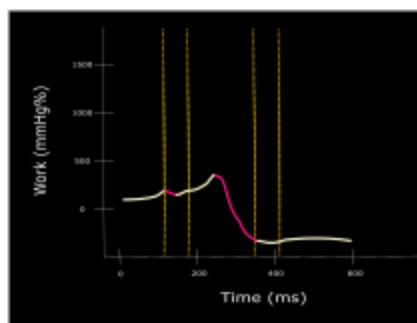
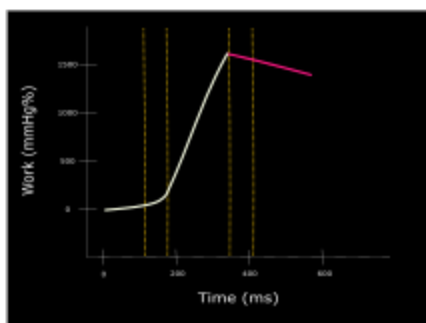
Blood pressure



Segmental pressure strain loops

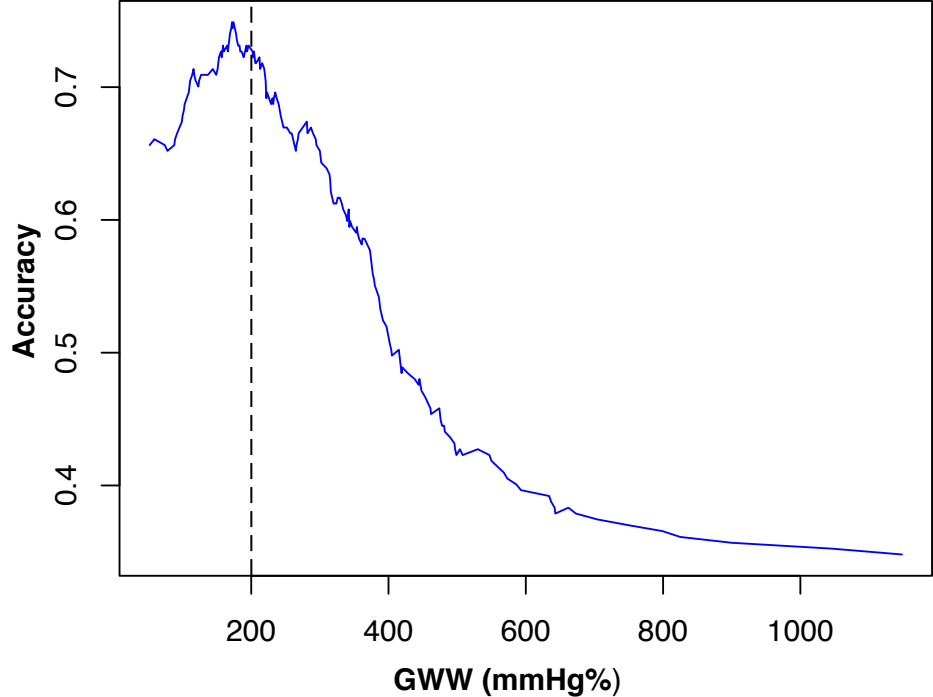


Segmental myocardial work Segmental wasted work

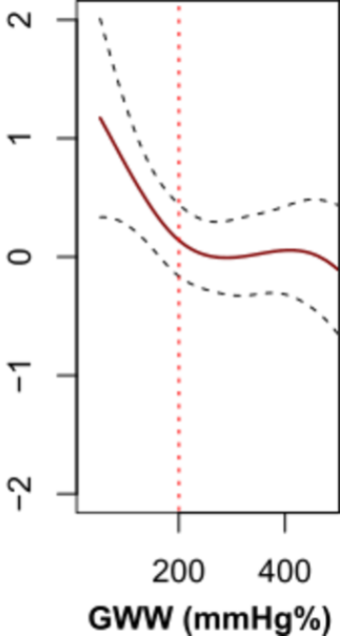


18 segments

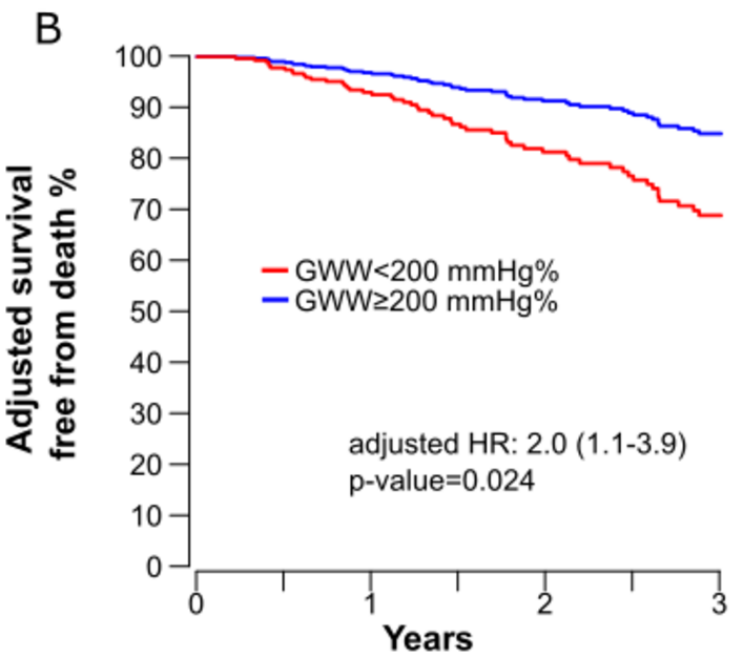
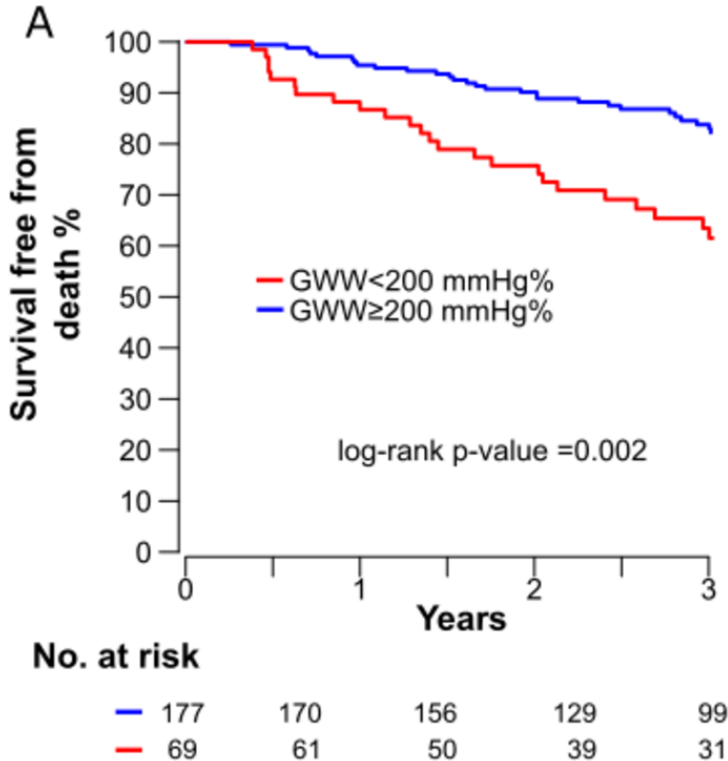
Global
Wasted Work

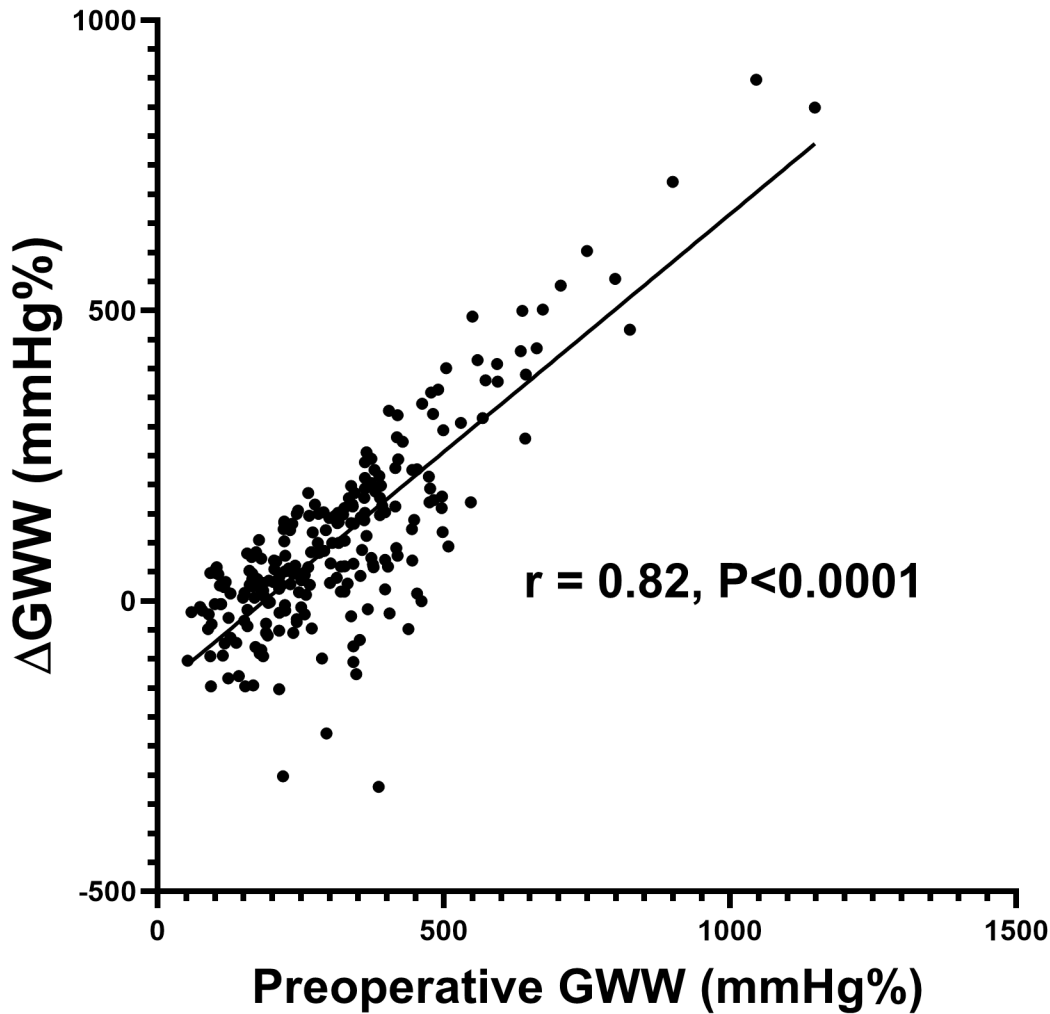


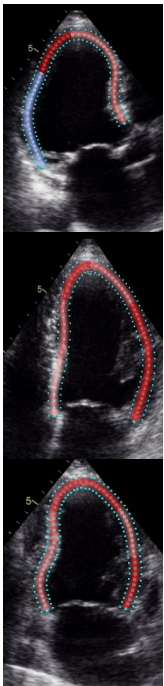
log relative hazard for death



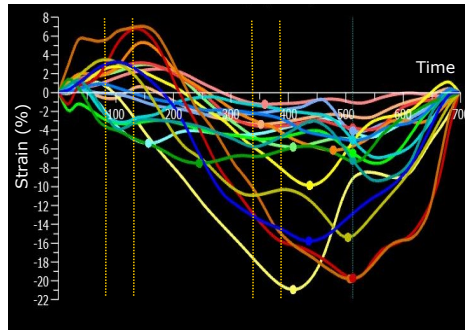
GWW (mmHg%)



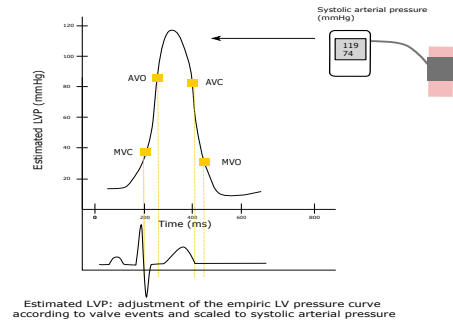




Global strain curves



Blood pressure



Global Wasted Work

