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**Myocardial constructive work and cardiac mortality in resynchronization therapy
candidates**

Short title: Constructive work and cardiac death in CRT

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ABSTRACT

Background: Recent studies have shown that myocardial constructive work (CW) assessed by pressure-strain loops (PSLs) is an independent predictor of a volumetric response to cardiac resynchronization therapy (CRT). Aim of this study was to evaluate the role of CW in predicting the cardiac outcome of heart failure patients undergoing CRT.

Methods: this is a retrospective study including 166 CRT-candidates (ejection fraction $\leq 35\%$, QRS duration ≥ 120 ms). 2D-standard and speckle-tracking echocardiography were performed before CRT and at 6-month follow-up (FU). PSLs were used to assess myocardial constructive work (CW).

Results: After a median FU of 4 years (range: 1.3-5 years), cardiac death occurred in 14 patients (8%). A multivariable Cox regression analysis including age, coronary artery disease (CAD), and septal flash (SF) showed that $CW \leq 888$ mmHg% was the only independent predictor of cardiac mortality (HR 4.23, 95% CI: 1.08-16.5, $p=0.03$). After 6 months of CRT, a 15% reduction in left ventricular end-systolic volume was observed in 118 (71%) patients, and a CRT volumetric response was identified. Among CRT-responders, the concomitant presence of $CW \leq 888$ mmHg% identified a subgroup of patients at high risk of cardiac death ($p=0.04$ in the log-rank test). The addition of $CW \leq 888$ mmHg% to a model including age, CAD, SF, and CRT response caused a significant increase in model power for the prediction of cardiac death (χ^2 : 12.6 vs 25.7, $p=0.02$).

Conclusions: The estimation of left ventricular CW by PSLs is a relatively novel tool that allows for the prediction of cardiac outcome in CRT candidates.

Highlights

- Pressure strain loops (PSL) allow the non-invasive estimation of myocardial work
- Myocardial constructive work has shown to be a predictor of CRT-response
- In CRT-candidates, myocardial constructive work is an independent predictor of cardiac death

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INTRODUCTION

Cardiac resynchronization therapy (CRT) has been demonstrated to improve the left ventricular (LV) function and outcomes of patients with both systolic heart failure (HF) and wide QRS (>120 ms)[1], whom remain symptomatic despite optimized medical therapy[2]. Despite these striking results, approximately one-third of patients do not benefit, and in some cases, may even be harmed after CRT[3]. Several studies have shown that in HF patients with wide QRS and regional mechanical discoordination derived from the estimation of LV mechanical delay, CRT might alleviate the mechanical dyssynchrony caused by LV electrical activation delay[4]. Nevertheless, the routine use of mechanical discoordination as an adjunct to the electrocardiographic criteria for the selection of CRT candidates has not gained clinical acceptance[5] and has been shown to even be detrimental in patients with normal QRS[6].

A potential explanation for these results is that the assessment of QRS duration and/or myocardial dyssynchrony does not take into account the role of residual myocardial contractility[7][8][9] as a potential source for LV functional restoration after CRT.

In recently published surveys[10][11] we demonstrated that the noninvasive estimation of global myocardial constructive work (CW) by PSL is a predictor of LV remodeling and response to CRT over common LV dyssynchrony parameters. The association between myocardial CW and outcome after CRT is, however, unknown. The aim of the present study was to assess the predictive role of myocardial CW on cardiac mortality in HF patients undergoing CRT.

METHODS

Population

This is a retrospective, observational, monocentric study conducted on 166 patients with systolic HF undergoing CRT implantation, according to current guidelines[1]. All patients

were in sinus rhythm and had a good acoustic window, allowing acquisition of 2D-echocardiography and speckle tracking echocardiography with excellent image quality. At the time of CRT implantation, all patients were receiving optimized medical therapy. Coronary artery disease (CAD) was defined as a history of myocardial infarction and coronary revascularization or angiographic evidence of multiple-vessel disease or single-vessel disease with $\geq 75\%$ stenosis of the left main or proximal left anterior descending artery[12]. CRT response was indicated by a decrease in LV end-systolic volume (ESV) $>15\%$ at the 6-month follow-up (FU)[5]. A biventricular stimulation $>90\%$ after CRT implantation was mandatory for patient inclusion in the protocol. Clinical data including age, sex, and treatments were collected for each patient. The functional status was assessed by the estimation of the New York Heart Association (NYHA) functional class. Data on the vital status of patients were collected from hospital medical records or by interview with the patients' general practitioner or relatives.

The study was conducted in accordance with the “Good Clinical Practice” guidelines of the Declaration of Helsinki and reviewed by an independent ethics committee (Regional Ethic Committee validation number: 35RC14-9767). All patients gave their written informed consent for study participation. No extramural funding was used to support this work.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents

Echocardiography

All patients underwent standard transthoracic echocardiography using a Vivid 7 or Vivid E9 and E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with a 3S or M5S 3.5-mHz transducer. Two-dimensional, color Doppler, pulsed-wave and continuous-wave Doppler data were stored on a dedicated workstation for the offline analysis (EchoPAC, GE

Healthcare, Horten, Norway). LV volumes and function were measured by the biplane method, as recommended[13].

Assessment of septal flash

The presence of septal flash (SF) was visually assessed before CRT implantation. SF was defined by the presence of an early septal thickening/thinning within the isovolumic contraction period[14][15].

Myocardial work quantification

Myocardial work and related indices were estimated using a vendor-specific module (EchoPAC Version 202, GE Vingmed Ultrasound, Norway). Myocardial work was estimated as a function of time throughout the cardiac cycle by the combination of LV strain data obtained by speckle tracking echocardiography and a noninvasively estimated LV pressure curve, as previously described by Russel et al.[16]. A 17-segment model was used for the estimation of segmental myocardial work.

The calculation of myocardial work followed several steps.

- 1) **LV strain analysis.** 2D grayscale images were acquired in the standard apical four-, three- and two-chamber views at a frame rate ≥ 60 frames/s, and the recordings were processed using an acoustic-tracking dedicated software (EchoPAC version 112.99, Research Release, GE Healthcare, Horten Norway) to estimate LV global longitudinal strain (GLS)[17]. Image quality for the enrolled patients was optimal, and no LV segments were excluded from strain analysis.
- 2) **Non invasive estimation of LV pressure (LVP).** The profile of an empiric LVP waveform provided by the software was used for the prediction of LVP in each specific subject by the analysis of aortic and mitral valve events (mitral valve closure, aortic valve opening, aortic valve closure, mitral valve opening) during the cardiac cycle. The duration of time intervals of isovolumic contraction, LV ejection, and isovolumic

relaxation was then determined by stretching or compressing the time axis of the averaged LVP curve to match the measured time intervals (Figure 1A, left side). The instantaneous systolic pressure value estimated by a brachial artery cuff was assumed to be equal to peak systolic LV pressure and to be uniform throughout the ventricle. This pressure value was then used to scale the normalized pressure signal in each patient (Figure 1B, right side). The reliability of this non-invasively estimated LV pressure curve was previously validated in a dog model [16], in CRT candidates, patients with dilated cardiomyopathy of ischemic and non-ischemic etiology [16][18][19], and in patients with arterial hypertension [19]

- 3) Calculation of myocardial work.** Strain and pressure data were synchronized using the R wave on ECG as a common time reference (Figure 1B, left side). Myocardial work was then quantified by calculating the rate of segmental shortening by differentiating the strain curve and multiplying the resulting value by the instantaneous LV-pressure (Figure 1B, right side). The result is a measure of instantaneous power, which was integrated over time to obtain myocardial work as a function of time. Work was calculated from mitral valve closure until mitral valve opening. During the isovolumic contraction and LV ejection period, segmental shortening contributes to the final LV ejection, whereas segmental stretch or lengthening do not contribute to LV ejection. As a result, the work performed by the myocardium during segmental shortening represents constructive work, whereas the work performed by the myocardium during stretch or segmental lengthening represents energy loss, which is defined as wasted work. During isovolumic relaxation, segmental lengthening contributes to LV relaxation, whereas segmental shortening doesn't. As a result, the work performed by the myocardium during segmental shortening, which doesn't promote LV relaxation, was considered wasted work, whereas the work performed by the myocardium during segmental lengthening was 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 (Figure 1B, right side)[16]. The overall process of estimation of myocardial work was quite fast, taking no more than 2 minutes after LV strain assessment. The inter-observer and intra-observer concordances for the estimation of myocardial work have already been reported[10],[11].

Statistical analysis

Continuous variables are expressed as the median and standard deviation and were compared using Student's t-test. Categorical data are expressed as frequencies and percentages and were compared by the χ^2 test. Receiver operator characteristics curve (ROC) analysis and the Youden's index were used to determine a CW cutoff that was able to predict events. Univariable Cox proportional hazards analysis of baseline clinical, electrocardiographic and echocardiographic characteristics was performed using cardiac mortality as endpoint. For each variable, the hazard ratio (HR) and 95% confidence intervals (CI) were calculated. Only variables with a p-value <0.05 in the univariable analysis were inserted in the multivariable Cox analysis. Freedom cardiac death was plotted for both CW groups using Kaplan-Meier curves. Between-group differences in freedom from events were tested using the log-rank test. Finally, the merits of CW over different nested models including clinical variables, SF, and CRT response to predict mortality were assessed with Cox regression analysis, and the incremental value of each model was assessed by the χ^2 test at each step, and by the Harrel's C-concordance statistics. Intra- and inter-observer reliability for the assessment of SF was estimated by the percentage of agreement and Cohen's κ in 20 randomly selected patients. All statistical analysis was performed using a standard statistical software program (SPSS Version 20.0, IBM, Chicago, IL, USA and R statistical software, version 3.4.4). A value of $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the population are summarized in Table 1. In the overall population, 48 (29%) patients had ischemic cardiomyopathy. LBBB was present in 136 (82%) patients. SF was identified in 105 (63%) patients. Intra- and interobserver agreement for visual assessment of SF were 95% ($\kappa=0.90$, [95%CI: 0.71-1], $p<0.0001$) and 90% ($\kappa=0.80$, [95% CI: 0.58-1], $p=0<0.0001$), respectively.

ROC curve analysis showed that a cutoff value of 888 mmHg% for CW was the best predictor of cardiac death (AUC 0.71, 95% CI: 0.60-0.82, $p=0.007$) (Figure 2). Patients with $CW\leq 888$ mmHg were more often male ($p=0.01$), had more dilated LV, lower LVEF and GLS (all $p<0.0001$), and lower prevalence of SF ($p=0.01$) than patients with $CW>888$ mmHg. A significantly lower rate of CRT responders was observed in this group ($p<0.0001$).

Clinical and echocardiographic data according to CRT response.

At the 6-month FU, volumetric CRT response occurred in 118 (71%) patients. Non-responders were more often male (81 vs 64%, $p=0.002$) and had a lower prevalence of LBBB (29 vs 77%, $p<0.0001$) and SF (67 vs 89%, $p=0.006$) than responders. A significant difference in indexed LV end-diastolic volume, LV end-systolic volume, LVEF, and CW was observed between the two groups at baseline and at 6-month FU. A significant improvement in LV geometry and function was observed in CRT-responders at the 6-month FU. On the contrary, a slight increase in the indexed LV end-systolic volume and decrease in WW were observed in non-responders (Table 2).

Follow-up

The median follow-up was 4 years (interquartile range: 1.3-5 years). During this time span, cardiac death occurred in 14 patients (8%); 13 patients died of refractory heart failure, and 1 died one week after a heart transplant. In the multivariable Cox regression analysis, CW was an independent predictor of cardiac death (Table 3, Model A).

Kaplan-Meier survival curves (Figure 3) showed that $CW \leq 888$ mmHg% was highly associated with a poor outcome (log-rank $p=0.008$). Patients with $CW \leq 888$ mmHg% had a higher risk of cardiac death (HR 4.76, 95% CI: 1.33-17.12, $p=0.01$) (Table 3). When $CW \leq 888$ mmHg% was used instead of the continuous variable to predict CRT response in the multivariable Cox regression analysis, it remained the only significant predictor of mortality (HR 4.23, 95% CI: 1.08-16.5, $p=0.03$).

Long-term outcome in relation to CRT response and septal flash

To compare the added value of CW over LV reverse remodeling for predicting the course of the disease, volumetric response to CRT was added to the Cox multivariable model (Table 3, Model B). In this model, CRT response was no longer a significant predictor of cardiac death, and it did not affect the HR of CW, which remained a significant predictor of cardiac mortality. Among responders, the presence of a $CW \leq 888$ mmHg% resulted in increased cardiac mortality, as shown by the log-rank test. The concomitant absence of volumetric response to CRT and $CW \leq 888$ mmHg% identified a subgroup of patients with a particularly dismal prognosis (Figure 4).

The relationship between CW and outcome was independent from SF (Table 2). In patients with SF, the presence of a $CW \leq 888$ mmHg% was associated with a significantly increased CV and all-cause mortality (log-rank test: $p=0.001$). Patients without SF and with $CW \leq 888$ mmHg% presented the worst prognosis (Figure 5).

Finally, to evaluate the predictive value of $CW \leq 888$ mmHg% over SF and CRT response for cardiac death, Cox regression analysis was used, and different nested models were created.

The incremental value of each model was assessed by comparing the χ^2 value at each step.

The accuracy of the Cox proportional hazards model in predicting cardiac mortality did not increase after adding SF and CRT response to clinical variables, but was significantly

increased by the addition of CW (Figure 6). Table 4 shows the Harrell's C-concordance statistic index for each model.

DISCUSSION

In the present study, we showed that in CRT candidates, the degree of global myocardial CW is a predictor of long-term survival, independent of the presence of SF and the volumetric response to CRT.

Assessment of myocardial constructive work

PSL curves are a recently introduced tool that allow a noninvasive estimation of myocardial work. The reliability of this method with respect to the invasive estimation of myocardial work has been validated by experimental studies and mathematical models[16][20][18]. Regional differences in myocardial work assessed by PSLs have a strong correlation with the entity of myocardial glucose metabolism evaluated by FDG-PET[16]. These results support the hypothesis that the differences in CW detected by PSLs before CRT correspond to myocardial residual metabolic activity and contractile reserve and might, therefore, explain the role of baseline CW in predicting CRT response[10],[11],[16] and long-term survival after CRT.

Myocardial constrictive work as a predictor of prognosis in CRT candidates

Although CRT has a pivotal role for the treatment of patients with HF and widened QRS, the lack of response to CRT remains an important clinical problem. From a physiologic point of view, it seems reasonable to believe that the main effect of CRT might be observed when a delayed electrical activation is associated with significant LV mechanical delay.

Nevertheless, the origin of LV mechanical discoordination may arise from substrates, such as a regional myocardial scar or hypocontractility, that are unresponsive to the electrical stimulation of CRT[9]. In patients with HF undergoing CRT, Ciampi et al. demonstrated that the presence of contractile reserve assessed by dobutamine stress echocardiography was

associated with a better prognosis independent of the presence of LV dyssynchrony[21]. In the present study, global CW was associated with CRT response and emerged as a predictor of long-term prognosis in CRT candidates; this result was independent of well-known predictors of CRT response, namely, QRS duration, left bundle-branch block, and SF.

The presence of LV dyssynchrony is traditionally considered a predictor of CRT response, and its correction by CRT is associated with good prognosis[14],[15]. In our observational study, patients with LV dyssynchrony identified by the presence of SF and $CW > 888$ mmHg% had the best outcomes, whereas the presence of $CW < 888$ mmHg% increased the risk of cardiac and all-cause death in patients with SF. The concomitant absence of SF and $CW \leq 888$ mmHg% was associated with a poor prognosis. These findings underscore the importance of the myocardial substrate of functional response beyond the assessment of LV dyssynchrony. Interestingly, the prognostic value of myocardial work persisted when CRT volumetric response is considered. In fact, the best prognosis was observed in CRT responders who also had a $CW > 888$ mmHg% before CRT implantation; the absence of response to CRT and a $CW \leq 888$ mmHg% was associated with the highest mortality.

Need for physiological understanding

The absence of myocardial viability is associated with the extent of LV remodeling before CRT and with the presence of extensive myocardial remodeling and fibrosis[22].

In our population, $CW \leq 888$ mmHg% was associated with a greater LV size and reduced LVEF before CRT. This cutoff identified a subgroup of patients with a particularly dismal prognosis and limited positive remodeling after CRT implantation.

The possibility that LV stimulation might gradually recruit viable myocardium might, therefore, be the key to achieving significant LV reverse remodeling after CRT and improved survival. Myocardial viability can be assessed by several methods, including MRI, stress echocardiography and nuclear imaging. PSLs allow the assessment of myocardial

performance in a rapid and effective manner and might, therefore, have a complementary role with respect to these costly investigations.

Speckle tracking echocardiography allows the simultaneous assessment of LV dyssynchrony, mechanical dispersion, and GLS. Previous studies have shown that the observation of LV mechanical dispersion in speckle tracking echocardiography is a predictor of ventricular arrhythmias in CRT candidates[23] and is related to LV fibrosis[24]. LV-GLS is also a well-known prognostic predictor in CRT candidates[23][25]. The assessment of myocardial work by PSLs can take into account the effect of afterload on LV function, which allows a comprehensive evaluation of LV performance.

Clinical perspectives

An increasing amount of data seem to underscore that the major benefits of CRT are observed when LV mechanical dyssynchrony is induced by an electrical activation delay. The results of the present study are not in opposition to this hypothesis but underscore the importance of the concomitant evaluation of the myocardial substrate of LV dysfunction in CRT candidates.

The existence of multiple independent mechanisms governing CRT response (e.g., ECG patterns, electromechanical delay, and residual contractility) supports the hypothesis that a multimodal stepwise approach that combines clinical, electrocardiographic, and echocardiographic data might be more effective for the identification of CRT responders. Moving in that direction, the use of myocardial work seems very promising: it integrates the load, it is an automatic measurement with associated robustness, and it could be used as a global and a regional myocardial function parameter.

Limitations

This is a monocentric, retrospective study aimed at assessing the relationship between CW and mortality in CRT candidates. With respect to previous studies, which often include all-

cause mortality and heart failure hospitalization in the primary end-point, we focused specifically on the predictors of cardiac mortality. The overall cardiac mortality rate in our survey was relatively low (4%), which might be attributed to the high percentage of CRT-responders (70%), the relatively low prevalence of ischemic cardiomyopathy (29%), and the significant increase in LVEF observed in responders (Table 2). No validation cohort was created to replicate our findings on myocardial work, which currently limits its application in everyday clinical practice. Precise myocardial scar localization and extension by cardiac MRI or nuclear imaging was not investigated in the current study, as far as the relationship between scar localization and LV lead position. Such investigations may be important to further understand the relationship between regional CW and LV function improvement in CRT candidates and should be the object of a future study.

As for many other echo-parameters, the proper assessment of myocardial work requires a suitable acoustic windows, and is not applicable to patients with poor echogenicity.

Until now, the validation of the non-invasive estimation of myocardial work by pressure-strain loops analysis has been restricted to patients to CRT candidates, patients with dilated cardiomyopathy of ischemic and non-ischemic etiology, and patients with arterial hypertension[16][18][19], which limits the reliable application of this method to these specific subsets of cardiac diseases.

CONCLUSIONS

CW assessed by PSLs is a recently introduced parameter that can predict long-term prognosis in CRT candidates. Patients with $CW \leq 888$ mmHg% had a 5-fold increased risk of cardiac death. Mortality prediction was improved over the classical predictors of CRT prognosis, including LV dyssynchrony and CRT volumetric response, and allows the identification of a subset of patients with a significantly dismal prognosis.

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Disclosures

Professor Smiseth is a co-inventor but no longer has ownership of the patent “Method for myocardial segment work analysis”, which was used to calculate myocardial work. The other authors report that there are no conflicts of interest.

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FIGURE CAPTIONS

Figure 1. The noninvasive LV pressure curve was obtained using an empiric, normalized reference curve that was adjusted according to the duration of the isovolumetric and ejection phases of the left ventricle, which were defined by the assessment of valvular events by echocardiography (A). Pressure data were then combined with left ventricular global longitudinal strain data using the R-wave onset in the electrocardiogram as a common time reference (B, left panel) and used for the estimation of myocardial work in each myocardial segment (B, right panel).

Figure 2. ROC curve analysis of left ventricular constructive work for the prediction of cardiac death.

Figure 3. Kaplan-Meier estimates of the time to cardiac death displayed according to CW cut-offs.

Figure 4. Kaplan-Meier estimates of the time to cardiac death in CRT-responders (CRT+) and non-responders (CRT-).

Figure 5. Kaplan-Meier estimates of the time to cardiac death in patients with septal flash (SF+) and without septal flash (SF-).

Figure 6. Incremental prognostic value of myocardial work on clinical variables, septal flash and CRT response.

Table 1: Baseline characteristics of the population

| Variables | All | CW> 888 mmHg% | CW≤888 | <i>p-value</i> |
|--|---------------------|---------------|----------------------|----------------|
| | patients (n=166) | (n=99, 60%) | mmHg% (n=67, 40%) | |
| Age, years | 66±10 | 66±10 | 64±11 | 0.19 |
| Male, n | 115 (69%) | 61 (62%) | 54 (81%) | 0.01 |
| Ischemic disease, n | 48 (29%) | 27 (27%) | 21 (31%) | 0.60 |
| NYHA>II | 70 (42%) | 40 (40%) | 30 (45%) | 0.52 |
| Arterial Hypertension | 32 (19%) | 18 (18%) | 13 (19%) | 0.31 |
| Diabetes | 17 (10%) | 6 (6%) | 11 (16%) | 0.05 |
| Dyslipidemia | 63 (38%) | 35 (35%) | 28 (42%) | 0.40 |
| Creatinine, $\mu\text{mol/L}$ | 99±31 | 95±30 | 104±31 | 0.07 |
| QRS widths, <i>per ms</i> | 165±19 | 163±16 | 169±23 | 0.07 |
| QRS> 150 ms | 124 (75%) | 75 (76%) | 49 (73%) | 0.55 |
| LBBB, n | 136 (82%) | 86 (87%) | 50 (75%) | 0.14 |
| LV-EF, % | 28±7 | 30±6 | 24±7 | <0.0001 |
| LV-EDV, ml/m^2 | 120±42 | 105±31 | 143±45 | <0.0001 |
| LV-ESV, ml/m^2 | 84±36 | 71±25 | 104±39 | <0.0001 |
| LV-GLS, % | -9±3 | -9±3 | -6±2 | <0.0001 |
| SF, n | 105 (63%) | 71 (72%) | 34 (51%) | 0.01 |
| Constructive Work, <i>per</i> mmHg% | 1025±442 | 1288±329 | 636±171 | <0.0001 |
| Wasted work, <i>per</i> mmHg% | 229±134 | 307±140 | 288±124 | 0.39 |
| CRT-responders, n | 118 (71%) | 81 (82%) | 37 (55%) | <0.0001 |

EDV; end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global

longitudinal strain; LBBB, Left Bundle Branch Block; LV, left ventricle; NYHA, New York

Heart Association functional class; SF, septal flash

Table 2. Comparative data on left ventricular size, function, and myocardial work in CRT-responders and non-responders at baseline and at 6-month follow-up

| | Responders | Non-responders | <i>p-value</i> |
|-------------------------------------|--------------------|-----------------------|----------------|
| | N=118 (71%) | N=48 (29%) | |
| <i>Baseline</i> | | | |
| LV-EDV, ml/m ² | 117±42 | 129±41 | 0.037 |
| LV-ESV, ml/m ² | 83±35 | 89±36 | 0.15 |
| LV-EF, % | 28±7 | 28±8 | 0.62 |
| LV-GLS, % | -9±3 | -7±3 | 0.0001 |
| Constructive work, mmHg% | 1104±434 | 838±324 | 0.0001 |
| Wasted work, mmHg% | 325±137 | 245±114 | 0.001 |
| <i>After 6 months of CRT</i> | | | |
| LV-EDV, ml/m ² | 80±28* | 129±38 | <0.0001 |
| LV-ESV, ml/m ² | 45±21* | 91±35† | <0.0001 |
| LV-EF, % | 45±11* | 28±9 | <0.0001 |
| LV-GLS, % | -13±4* | -8±4 | <0.0001 |
| Constructive work, mmHg% | 1452±420* | 920±372 | <0.0001 |
| Wasted work, mmHg% | 197±111* | 197±102† | 0.99 |

*p<0.0001 with respect to Baseline

†<0.05 with respect to Baseline

Table 3. Predictors of cardiac death at univariable and multivariable analysis. Two multivariate models were created: Model A not including CRT-reponse and Model B including CRT response

| | Univariable analysis | | | Multivariable analysis | | | | | |
|--------------------------------------|----------------------|--------------|----------|------------------------|--------------|----------|---------|-------------|----------|
| | HR | 95% CI | <i>p</i> | Model A | | | Model B | | |
| | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> |
| Age, <i>per year</i> | 1.08 | (1.01-1.15) | 0.02 | 1.07 | (1.00-1.14) | 0.05 | 1.07 | (1.00-1.15) | 0.04 |
| Male sex | 1.75 | (0.49-6.27) | 0.39 | | | | | | |
| Ischaemic disease | 3.99 | (1.34-11.94) | 0.01 | 2.99 | (0.79-11.16) | 0.10 | 2.33 | (0.71-1.15) | 0.16 |
| NYHA>2 | 1.39 | (0.46-4.24) | 0.56 | | | | | | |
| Arterial Hypertension | 0.81 | (0.22-2.95) | 0.75 | | | | | | |
| Diabetes | 2.56 | (0.69-9.45) | 0.16 | | | | | | |
| Dyslipidemia | 1.49 | (0.49-4.56) | 0.49 | | | | | | |
| Creatinine, <i>per μmol/L</i> | 1.01 | (0.99-1.93) | 0.07 | | | | | | |
| QRS duration, <i>per ms</i> | 0.99 | (0.97-1.03) | 0.81 | | | | | | |
| QRS>150 ms | 0.48 | (0.17-0.40) | 0.18 | | | | | | |
| LBBB | 0.87 | (0.27-2.77) | 0.81 | | | | | | |
| LVEF, <i>per %</i> | 0.99 | (0.92-1.08) | 0.89 | | | | | | |
| LVEDV, <i>per ml/m²</i> | 1.01 | (0.99-1.02) | 0.46 | | | | | | |
| LVESV, <i>per ml/m²</i> | 1.01 | (0.99-1.02) | 0.69 | | | | | | |
| Septal flash | 0.19 | (0.06-0.62) | 0.006 | 2.29 | (0.54-9.71) | 0.26 | 0.48 | (0.12-1.95) | 0.30 |
| LV-GLS | 1.21 | (0.99-1.47) | 0.06 | | | | | | |
| Wasted work, <i>per mmHg%</i> | 0.99 | (0.99-1.01) | 0.75 | | | | | | |
| Constructive Work, <i>per mmHg%*</i> | 0.99 | (0.99-1.00) | 0.04 | 0.99 | (0.99-1.01) | 0.03 | 0.99 | (0.99-1.00) | 0.04 |
| Constuctive Work ≤888 mmHg% | 4.76 | (1.33-17.12) | 0.01 | | | | | | |
| CRT-response** | 0.26 | (0.09-0.78) | 0.02 | | | | 0.68 | (0.18-2.57) | 0.58 |

CI, confidence interval; CRT-response, cardiac resynchronization therapy positive response;
HR, hazard ratio

*The continuous variable was inserted in the multivariate analysis

** CRT-response was added to multivariate analysis in Model B, but not in Model A.

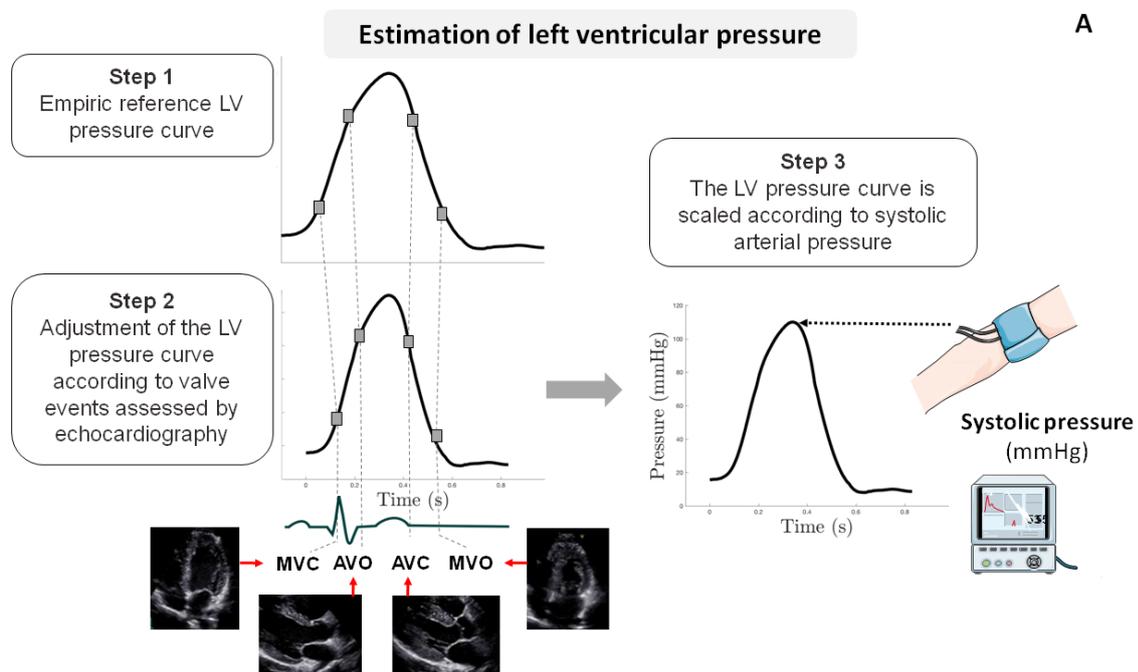
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Table 4. Incremental Prognostic Value of clinical parameters, CRT response, and myocardial constructive work: Discrimination Index Analysis

| | | Harrell's C-concordance |
|----------------|--------------------|-------------------------|
| Model 1 | Age | 0.73 |
| | Ischaemic disease | |
| Model 2 | Age | 0.75 |
| | Ischemic disease | |
| | Septal flash | |
| Model 3 | Age | 0.76 |
| | Ischemic disease | |
| | Septal flash | |
| | CRT response | |
| Model 4 | Age | 0.82 |
| | Ischemic disease | |
| | CRT response | |
| | Septal flash | |
| | CW \leq 888 mmHg | |

Figures

Figure 1A



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Figure 1B

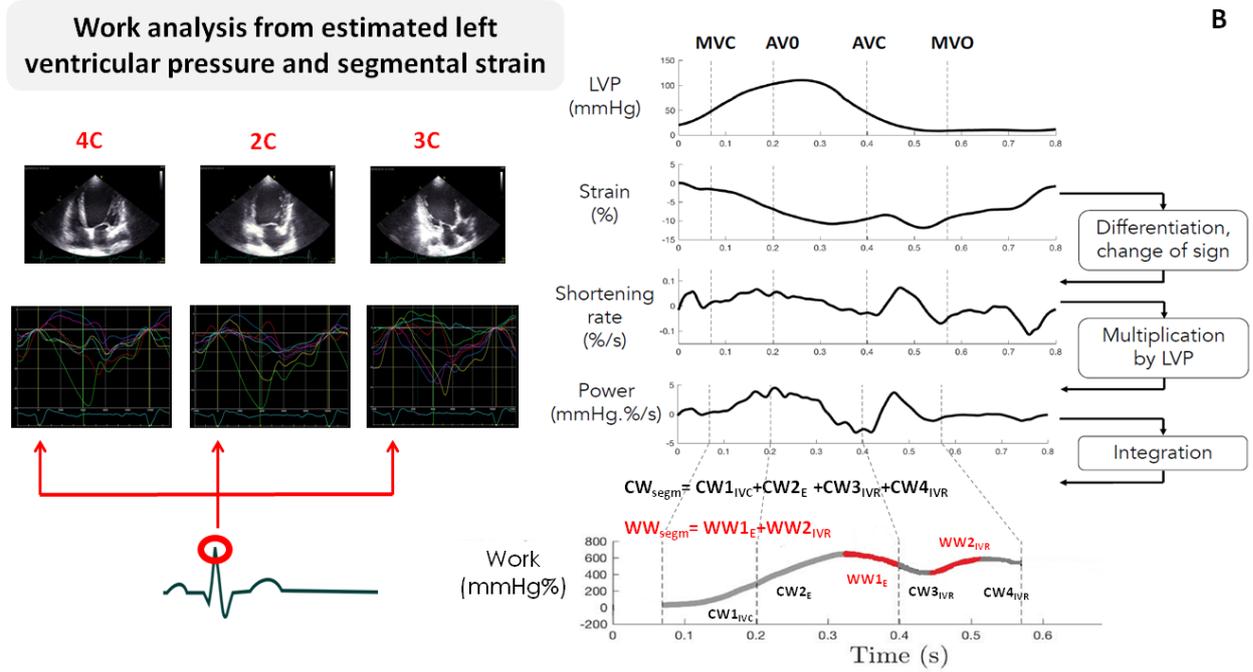
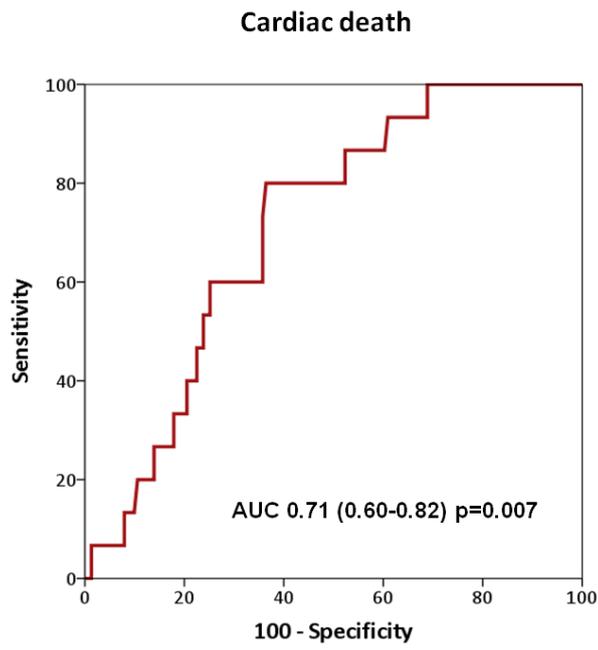
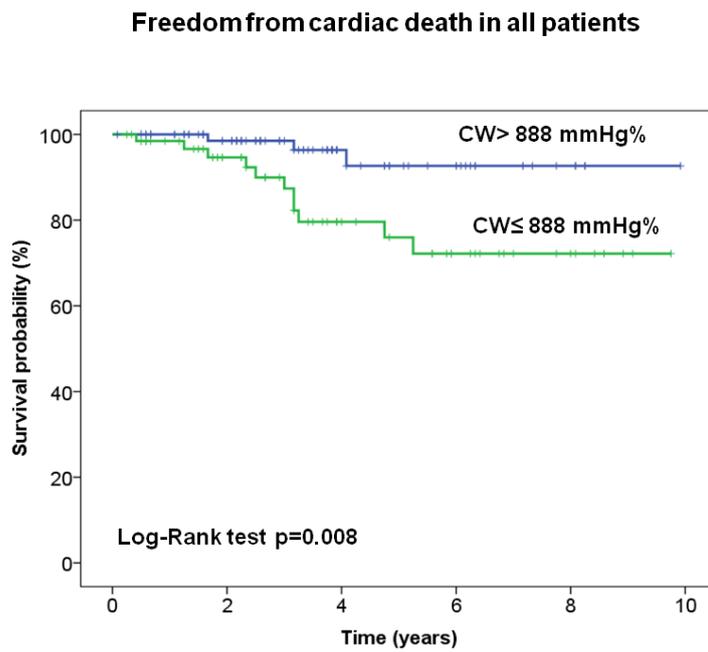


Figure 2



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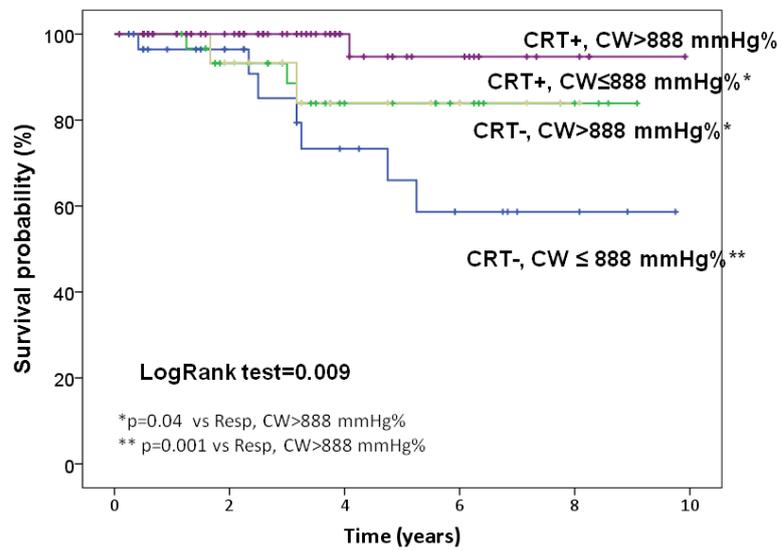
Figure 3



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Figure 4

Freedom from cardiac death according to CW and CRT response



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Figure 5

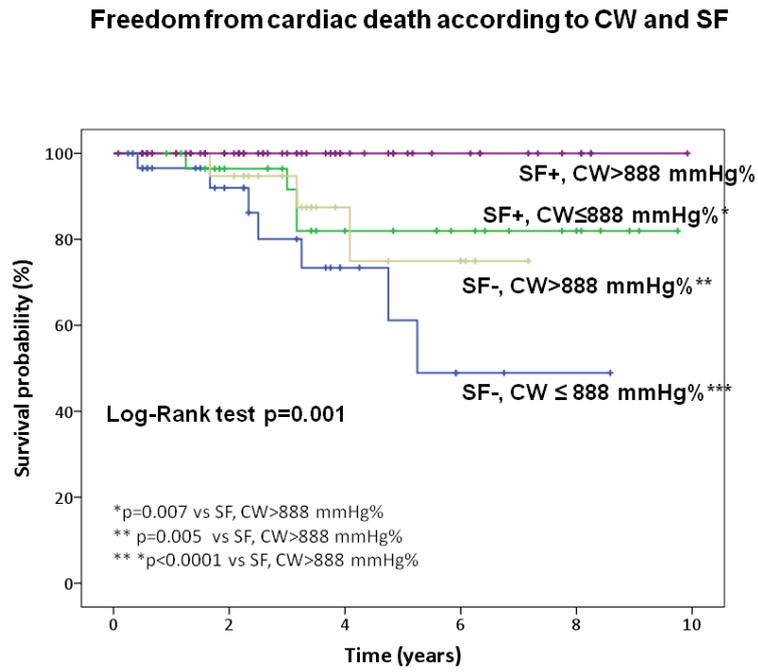
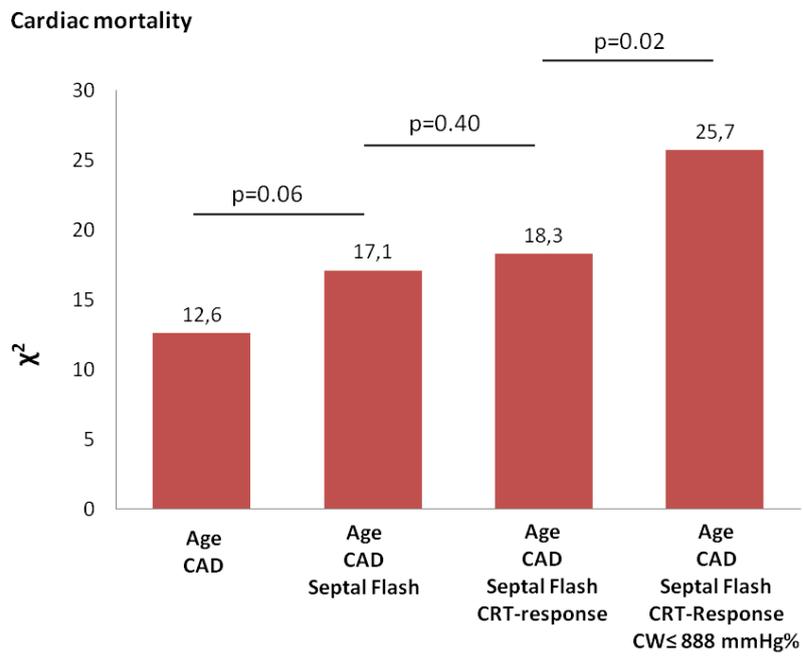


Figure 6



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**Myocardial constructive work and cardiac mortality in resynchronization therapy
candidates**

Short title: Constructive work and cardiac death in CRT

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Keywords: cardiac resynchronization therapy, cardiac mortality, myocardial constructive work.

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ABSTRACT

Background: Recent studies have shown that myocardial constructive work (CW) assessed by pressure-strain loops (PSLs) is an independent predictor of a volumetric response to cardiac resynchronization therapy (CRT). Aim of this study was to evaluate the role of CW in predicting the cardiac outcome of heart failure patients undergoing CRT.

Methods: this is a retrospective study including 166 CRT-candidates (ejection fraction $\leq 35\%$, QRS duration ≥ 120 ms). 2D-standard and speckle-tracking echocardiography were performed before CRT and at 6-month follow-up (FU). PSLs were used to assess myocardial constructive work (CW).

Results: After a median FU of 4 years (range: 1.3-5 years), cardiac death occurred in 14 patients (8%). A multivariable Cox regression analysis including age, coronary artery disease (CAD), and septal flash (SF) showed that $CW \leq 888$ mmHg% was the only independent predictor of cardiac mortality (HR 4.23, 95% CI: 1.08-16.5, $p=0.03$). After 6 months of CRT, a 15% reduction in left ventricular end-systolic volume was observed in 118 (71%) patients, and a CRT volumetric response was identified. Among CRT-responders, the concomitant presence of $CW \leq 888$ mmHg% identified a subgroup of patients at high risk of cardiac death ($p=0.04$ in the log-rank test). The addition of $CW \leq 888$ mmHg% to a model including age, CAD, SF, and CRT response caused a significant increase in model power for the prediction of cardiac death (χ^2 : 12.6 vs 25.7, $p=0.02$).

Conclusions: The estimation of left ventricular CW by PSLs is a relatively novel tool that allows for the prediction of cardiac outcome in CRT candidates.

Highlights

- Pressure strain loops (PSL) allow the non-invasive estimation of myocardial work
- Myocardial constructive work has shown to be a predictor of CRT-response
- In CRT-candidates, myocardial constructive work is an independent predictor of cardiac death

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INTRODUCTION

Cardiac resynchronization therapy (CRT) has been demonstrated to improve the left ventricular (LV) function and outcomes of patients with both systolic heart failure (HF) and wide QRS (>120 ms)[1], whom remain symptomatic despite optimized medical therapy[2]. Despite these striking results, approximately one-third of patients do not benefit, and in some cases, may even be harmed after CRT[3]. Several studies have shown that in HF patients with wide QRS and regional mechanical discoordination derived from the estimation of LV mechanical delay, CRT might alleviate the mechanical dyssynchrony caused by LV electrical activation delay[4]. Nevertheless, the routine use of mechanical discoordination as an adjunct to the electrocardiographic criteria for the selection of CRT candidates has not gained clinical acceptance[5] and has been shown to even be detrimental in patients with normal QRS[6].

A potential explanation for these results is that the assessment of QRS duration and/or myocardial dyssynchrony does not take into account the role of residual myocardial contractility[7][8][9] as a potential source for LV functional restoration after CRT.

In recently published surveys[10][11] we demonstrated that the noninvasive estimation of global myocardial constructive work (CW) by PSL is a predictor of LV remodeling and response to CRT over common LV dyssynchrony parameters. The association between myocardial CW and outcome after CRT is, however, unknown. The aim of the present study was to assess the predictive role of myocardial CW on cardiac mortality in HF patients undergoing CRT.

METHODS

Population

This is a retrospective, observational, monocentric study conducted on 166 patients with systolic HF undergoing CRT implantation, according to current guidelines[1]. All patients

were in sinus rhythm and had a good acoustic window, allowing acquisition of 2D-echocardiography and speckle tracking echocardiography with excellent image quality. At the time of CRT implantation, all patients were receiving optimized medical therapy. Coronary artery disease (CAD) was defined as a history of myocardial infarction and coronary revascularization or angiographic evidence of multiple-vessel disease or single-vessel disease with $\geq 75\%$ stenosis of the left main or proximal left anterior descending artery[12]. CRT response was indicated by a decrease in LV end-systolic volume (ESV) $>15\%$ at the 6-month follow-up (FU)[5]. A biventricular stimulation $>90\%$ after CRT implantation was mandatory for patient inclusion in the protocol. Clinical data including age, sex, and treatments were collected for each patient. The functional status was assessed by the estimation of the New York Heart Association (NYHA) functional class. Data on the vital status of patients were collected from hospital medical records or by interview with the patients' general practitioner or relatives.

The study was conducted in accordance with the “Good Clinical Practice” guidelines of the Declaration of Helsinki and reviewed by an independent ethics committee (Regional Ethic Committee validation number: 35RC14-9767). All patients gave their written informed consent for study participation. No extramural funding was used to support this work.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents

Echocardiography

All patients underwent standard transthoracic echocardiography using a Vivid 7 or Vivid E9 and E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with a 3S or M5S 3.5-mHz transducer. Two-dimensional, color Doppler, pulsed-wave and continuous-wave Doppler data were stored on a dedicated workstation for the offline analysis (EchoPAC, GE

Healthcare, Horten, Norway). LV volumes and function were measured by the biplane method, as recommended[13].

Assessment of septal flash

The presence of septal flash (SF) was visually assessed before CRT implantation. SF was defined by the presence of an early septal thickening/thinning within the isovolumic contraction period[14][15].

Myocardial work quantification

Myocardial work and related indices were estimated using a vendor-specific module (EchoPAC Version 202, GE Vingmed Ultrasound, Norway). Myocardial work was estimated as a function of time throughout the cardiac cycle by the combination of LV strain data obtained by speckle tracking echocardiography and a noninvasively estimated LV pressure curve, as previously described by Russel et al.[16]. A 17-segment model was used for the estimation of segmental myocardial work.

The calculation of myocardial work followed several steps.

- 4) **LV strain analysis.** 2D grayscale images were acquired in the standard apical four-, three- and two-chamber views at a frame rate ≥ 60 frames/s, and the recordings were processed using an acoustic-tracking dedicated software (EchoPAC version 112.99, Research Release, GE Healthcare, Horten Norway) to estimate LV global longitudinal strain (GLS)[17]. Image quality for the enrolled patients was optimal, and no LV segments were excluded from strain analysis.
- 5) **Non invasive estimation of LV pressure (LVP).** The profile of an empiric LVP waveform provided by the software was used for the prediction of LVP in each specific subject by the analysis of aortic and mitral valve events (mitral valve closure, aortic valve opening, aortic valve closure, mitral valve opening) during the cardiac cycle. The duration of time intervals of isovolumic contraction, LV ejection, and isovolumic

relaxation was then determined by stretching or compressing the time axis of the averaged LVP curve to match the measured time intervals (Figure 1A, left side). The instantaneous systolic pressure value estimated by a brachial artery cuff was assumed to be equal to peak systolic LV pressure and to be uniform throughout the ventricle. This pressure value was then used to scale the normalized pressure signal in each patient (Figure 1B, right side). The reliability of this non-invasively estimated LV pressure curve was previously validated in a dog model [16], in CRT candidates, patients with dilated cardiomyopathy of ischemic and non-ischemic etiology [16][18][19], and in patients with arterial hypertension [19]

- 6) **Calculation of myocardial work.** Strain and pressure data were synchronized using the R wave on ECG as a common time reference (Figure 1B, left side). Myocardial work was then quantified by calculating the rate of segmental shortening by differentiating the strain curve and multiplying the resulting value by the instantaneous LV-pressure (Figure 1B, right side). The result is a measure of instantaneous power, which was integrated over time to obtain myocardial work as a function of time. Work was calculated from mitral valve closure until mitral valve opening. During the isovolumic contraction and LV ejection period, segmental shortening contributes to the final LV ejection, whereas segmental stretch or lengthening do not contribute to LV ejection. As a result, the work performed by the myocardium during segmental shortening represents constructive work, whereas the work performed by the myocardium during stretch or segmental lengthening represents energy loss, which is defined as wasted work. During isovolumic relaxation, segmental lengthening contributes to LV relaxation, whereas segmental shortening doesn't. As a result, the work performed by the myocardium during segmental shortening, which doesn't promote LV relaxation, was considered wasted work, whereas the work performed by the myocardium during segmental lengthening was 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 (Figure 1B, right side)[16]. The overall process of estimation of myocardial work was quite fast, taking no more than 2 minutes after LV strain assessment. The inter-observer and intra-observer concordances for the estimation of myocardial work have already been reported[10],[11].

Statistical analysis

Continuous variables are expressed as the median and standard deviation and were compared using Student's t-test. Categorical data are expressed as frequencies and percentages and were compared by the χ^2 test. Receiver operator characteristics curve (ROC) analysis and the Youden's index were used to determine a CW cutoff that was able to predict events. Univariable Cox proportional hazards analysis of baseline clinical, electrocardiographic and echocardiographic characteristics was performed using cardiac mortality as endpoint. For each variable, the hazard ratio (HR) and 95% confidence intervals (CI) were calculated. Only variables with a p-value <0.05 in the univariable analysis were inserted in the multivariable Cox analysis. Freedom cardiac death was plotted for both CW groups using Kaplan-Meier curves. Between-group differences in freedom from events were tested using the log-rank test. Finally, the merits of CW over different nested models including clinical variables, SF, and CRT response to predict mortality were assessed with Cox regression analysis, and the incremental value of each model was assessed by the χ^2 test at each step, and by the Harrel's C-concordance statistics. Intra- and inter-observer reliability for the assessment of SF was estimated by the percentage of agreement and Cohen's κ in 20 randomly selected patients. All statistical analysis was performed using a standard statistical software program (SPSS Version 20.0, IBM, Chicago, IL, USA and R statistical software, version 3.4.4). A value of $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the population are summarized in Table 1. In the overall population, 48 (29%) patients had ischemic cardiomyopathy. LBBB was present in 136 (82%) patients. SF was identified in 105 (63%) patients. Intra- and interobserver agreement for visual assessment of SF were 95% ($\kappa=0.90$, [95%CI: 0.71-1], $p<0.0001$) and 90% ($\kappa=0.80$, [95% CI: 0.58-1], $p=0<0.0001$), respectively.

ROC curve analysis showed that a cutoff value of 888 mmHg% for CW was the best predictor of cardiac death (AUC 0.71, 95% CI: 0.60-0.82, $p=0.007$) (Figure 2). Patients with $CW\leq 888$ mmHg were more often male ($p=0.01$), had more dilated LV, lower LVEF and GLS (all $p<0.0001$), and lower prevalence of SF ($p=0.01$) than patients with $CW>888$ mmHg. A significantly lower rate of CRT responders was observed in this group ($p<0.0001$).

Clinical and echocardiographic data according to CRT response.

At the 6-month FU, volumetric CRT response occurred in 118 (71%) patients. Non-responders were more often male (81 vs 64%, $p=0.002$) and had a lower prevalence of LBBB (29 vs 77%, $p<0.0001$) and SF (67 vs 89%, $p=0.006$) than responders. A significant difference in indexed LV end-diastolic volume, LV end-systolic volume, LVEF, and CW was observed between the two groups at baseline and at 6-month FU. A significant improvement in LV geometry and function was observed in CRT-responders at the 6-month FU. On the contrary, a slight increase in the indexed LV end-systolic volume and decrease in WW were observed in non-responders (Table 2).

Follow-up

The median follow-up was 4 years (interquartile range: 1.3-5 years). During this time span, cardiac death occurred in 14 patients (8%); 13 patients died of refractory heart failure, and 1 died one week after a heart transplant. In the multivariable Cox regression analysis, CW was an independent predictor of cardiac death (Table 3, Model A).

Kaplan-Meier survival curves (Figure 3) showed that $CW \leq 888$ mmHg% was highly associated with a poor outcome (log-rank $p=0.008$). Patients with $CW \leq 888$ mmHg% had a higher risk of cardiac death (HR 4.76, 95% CI: 1.33-17.12, $p=0.01$) (Table 3). When $CW \leq 888$ mmHg% was used instead of the continuous variable to predict CRT response in the multivariable Cox regression analysis, it remained the only significant predictor of mortality (HR 4.23, 95% CI: 1.08-16.5, $p=0.03$).

Long-term outcome in relation to CRT response and septal flash

To compare the added value of CW over LV reverse remodeling for predicting the course of the disease, volumetric response to CRT was added to the Cox multivariable model (Table 3, Model B). In this model, CRT response was no longer a significant predictor of cardiac death, and it did not affect the HR of CW, which remained a significant predictor of cardiac mortality. Among responders, the presence of a $CW \leq 888$ mmHg% resulted in increased cardiac mortality, as shown by the log-rank test. The concomitant absence of volumetric response to CRT and $CW \leq 888$ mmHg% identified a subgroup of patients with a particularly dismal prognosis (Figure 4).

The relationship between CW and outcome was independent from SF (Table 2). In patients with SF, the presence of a $CW \leq 888$ mmHg% was associated with a significantly increased CV and all-cause mortality (log-rank test: $p=0.001$). Patients without SF and with $CW \leq 888$ mmHg% presented the worst prognosis (Figure 5).

Finally, to evaluate the predictive value of $CW \leq 888$ mmHg% over SF and CRT response for cardiac death, Cox regression analysis was used, and different nested models were created.

The incremental value of each model was assessed by comparing the χ^2 value at each step.

The accuracy of the Cox proportional hazards model in predicting cardiac mortality did not increase after adding SF and CRT response to clinical variables, but was significantly

increased by the addition of CW (Figure 6). Table 4 shows the Harrell's C-concordance statistic index for each model.

DISCUSSION

In the present study, we showed that in CRT candidates, the degree of global myocardial CW is a predictor of long-term survival, independent of the presence of SF and the volumetric response to CRT.

Assessment of myocardial constructive work

PSL curves are a recently introduced tool that allow a noninvasive estimation of myocardial work. The reliability of this method with respect to the invasive estimation of myocardial work has been validated by experimental studies and mathematical models[16][20][18]. Regional differences in myocardial work assessed by PSLs have a strong correlation with the entity of myocardial glucose metabolism evaluated by FDG-PET[16]. These results support the hypothesis that the differences in CW detected by PSLs before CRT correspond to myocardial residual metabolic activity and contractile reserve and might, therefore, explain the role of baseline CW in predicting CRT response[10],[11],[16] and long-term survival after CRT.

Myocardial constrictive work as a predictor of prognosis in CRT candidates

Although CRT has a pivotal role for the treatment of patients with HF and widened QRS, the lack of response to CRT remains an important clinical problem. From a physiologic point of view, it seems reasonable to believe that the main effect of CRT might be observed when a delayed electrical activation is associated with significant LV mechanical delay.

Nevertheless, the origin of LV mechanical discoordination may arise from substrates, such as a regional myocardial scar or hypocontractility, that are unresponsive to the electrical stimulation of CRT[9]. In patients with HF undergoing CRT, Ciampi et al. demonstrated that the presence of contractile reserve assessed by dobutamine stress echocardiography was

associated with a better prognosis independent of the presence of LV dyssynchrony[21]. In the present study, global CW was associated with CRT response and emerged as a predictor of long-term prognosis in CRT candidates; this result was independent of well-known predictors of CRT response, namely, QRS duration, left bundle-branch block, and SF.

The presence of LV dyssynchrony is traditionally considered a predictor of CRT response, and its correction by CRT is associated with good prognosis[14],[15]. In our observational study, patients with LV dyssynchrony identified by the presence of SF and $CW > 888$ mmHg% had the best outcomes, whereas the presence of $CW < 888$ mmHg% increased the risk of cardiac and all-cause death in patients with SF. The concomitant absence of SF and $CW \leq 888$ mmHg% was associated with a poor prognosis. These findings underscore the importance of the myocardial substrate of functional response beyond the assessment of LV dyssynchrony. Interestingly, the prognostic value of myocardial work persisted when CRT volumetric response is considered. In fact, the best prognosis was observed in CRT responders who also had a $CW > 888$ mmHg% before CRT implantation; the absence of response to CRT and a $CW \leq 888$ mmHg% was associated with the highest mortality.

Need for physiological understanding

The absence of myocardial viability is associated with the extent of LV remodeling before CRT and with the presence of extensive myocardial remodeling and fibrosis[22].

In our population, $CW \leq 888$ mmHg% was associated with a greater LV size and reduced LVEF before CRT. This cutoff identified a subgroup of patients with a particularly dismal prognosis and limited positive remodeling after CRT implantation.

The possibility that LV stimulation might gradually recruit viable myocardium might, therefore, be the key to achieving significant LV reverse remodeling after CRT and improved survival. Myocardial viability can be assessed by several methods, including MRI, stress echocardiography and nuclear imaging. PSLs allow the assessment of myocardial

performance in a rapid and effective manner and might, therefore, have a complementary role with respect to these costly investigations.

Speckle tracking echocardiography allows the simultaneous assessment of LV dyssynchrony, mechanical dispersion, and GLS. Previous studies have shown that the observation of LV mechanical dispersion in speckle tracking echocardiography is a predictor of ventricular arrhythmias in CRT candidates[23] and is related to LV fibrosis[24]. LV-GLS is also a well-known prognostic predictor in CRT candidates[23][25]. The assessment of myocardial work by PSLs can take into account the effect of afterload on LV function, which allows a comprehensive evaluation of LV performance.

Clinical perspectives

An increasing amount of data seem to underscore that the major benefits of CRT are observed when LV mechanical dyssynchrony is induced by an electrical activation delay. The results of the present study are not in opposition to this hypothesis but underscore the importance of the concomitant evaluation of the myocardial substrate of LV dysfunction in CRT candidates.

The existence of multiple independent mechanisms governing CRT response (e.g., ECG patterns, electromechanical delay, and residual contractility) supports the hypothesis that a multimodal stepwise approach that combines clinical, electrocardiographic, and echocardiographic data might be more effective for the identification of CRT responders. Moving in that direction, the use of myocardial work seems very promising: it integrates the load, it is an automatic measurement with associated robustness, and it could be used as a global and a regional myocardial function parameter.

Limitations

This is a monocentric, retrospective study aimed at assessing the relationship between CW and mortality in CRT candidates. With respect to previous studies, which often include all-

cause mortality and heart failure hospitalization in the primary end-point, we focused specifically on the predictors of cardiac mortality. The overall cardiac mortality rate in our survey was relatively low (4%), which might be attributed to the high percentage of CRT-responders (70%), the relatively low prevalence of ischemic cardiomyopathy (29%), and the significant increase in LVEF observed in responders (Table 2). No validation cohort was created to replicate our findings on myocardial work, which currently limits its application in everyday clinical practice. Precise myocardial scar localization and extension by cardiac MRI or nuclear imaging was not investigated in the current study, as far as the relationship between scar localization and LV lead position. Such investigations may be important to further understand the relationship between regional CW and LV function improvement in CRT candidates and should be the object of a future study.

As for many other echo-parameters, the proper assessment of myocardial work requires a suitable acoustic windows, and is not applicable to patients with poor echogenicity.

Until now, the validation of the non-invasive estimation of myocardial work by pressure-strain loops analysis has been restricted to patients to CRT candidates, patients with dilated cardiomyopathy of ischemic and non-ischemic etiology, and patients with arterial hypertension[16][18][19], which limits the reliable application of this method to these specific subsets of cardiac diseases.

CONCLUSIONS

CW assessed by PSLs is a recently introduced parameter that can predict long-term prognosis in CRT candidates. Patients with $CW \leq 888$ mmHg% had a 5-fold increased risk of cardiac death. Mortality prediction was improved over the classical predictors of CRT prognosis, including LV dyssynchrony and CRT volumetric response, and allows the identification of a subset of patients with a significantly dismal prognosis.

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Disclosures

Professor Smiseth is a co-inventor but no longer has ownership of the patent “Method for myocardial segment work analysis”, which was used to calculate myocardial work. The other authors report that there are no conflicts of interest.

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FIGURE CAPTIONS

Figure 1. The noninvasive LV pressure curve was obtained using an empiric, normalized reference curve that was adjusted according to the duration of the isovolumetric and ejection phases of the left ventricle, which were defined by the assessment of valvular events by echocardiography (A). Pressure data were then combined with left ventricular global longitudinal strain data using the R-wave onset in the electrocardiogram as a common time reference (B, left panel) and used for the estimation of myocardial work in each myocardial segment (B, right panel).

Figure 2. ROC curve analysis of left ventricular constructive work for the prediction of cardiac death.

Figure 3. Kaplan-Meier estimates of the time to cardiac death displayed according to CW cut-offs.

Figure 4. Kaplan-Meier estimates of the time to cardiac death in CRT-responders (CRT+) and non-responders (CRT-).

Figure 5. Kaplan-Meier estimates of the time to cardiac death in patients with septal flash (SF+) and without septal flash (SF-).

Figure 6. Incremental prognostic value of myocardial work on clinical variables, septal flash and CRT response.

Table 1: Baseline characteristics of the population

| Variables | All patients (n=166) | CW> 888 mmHg% (n=99, 60%) | CW≤888 mmHg% (n=67, 40%) | <i>p-value</i> |
|--|----------------------------|------------------------------|--------------------------------|----------------|
| Age, years | 66±10 | 66±10 | 64±11 | 0.19 |
| Male, n | 115 (69%) | 61 (62%) | 54 (81%) | 0.01 |
| Ischemic disease, n | 48 (29%) | 27 (27%) | 21 (31%) | 0.60 |
| NYHA>II | 70 (42%) | 40 (40%) | 30 (45%) | 0.52 |
| Arterial Hypertension | 32 (19%) | 18 (18%) | 13 (19%) | 0.31 |
| Diabetes | 17 (10%) | 6 (6%) | 11 (16%) | 0.05 |
| Dyslipidemia | 63 (38%) | 35 (35%) | 28 (42%) | 0.40 |
| Creatinine, $\mu\text{mol/L}$ | 99±31 | 95±30 | 104±31 | 0.07 |
| QRS widths, <i>per ms</i> | 165±19 | 163±16 | 169±23 | 0.07 |
| QRS> 150 ms | 124 (75%) | 75 (76%) | 49 (73%) | 0.55 |
| LBBB, n | 136 (82%) | 86 (87%) | 50 (75%) | 0.14 |
| LV-EF, % | 28±7 | 30±6 | 24±7 | <0.0001 |
| LV-EDV, ml/m^2 | 120±42 | 105±31 | 143±45 | <0.0001 |
| LV-ESV, ml/m^2 | 84±36 | 71±25 | 104±39 | <0.0001 |
| LV-GLS, % | -9±3 | -9±3 | -6±2 | <0.0001 |
| SF, n | 105 (63%) | 71 (72%) | 34 (51%) | 0.01 |
| Constructive Work, <i>per</i> mmHg% | 1025±442 | 1288±329 | 636±171 | <0.0001 |
| Wasted work, <i>per</i> mmHg% | 229±134 | 307±140 | 288±124 | 0.39 |
| CRT-responders, n | 118 (71%) | 81 (82%) | 37 (55%) | <0.0001 |

EDV; end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global

longitudinal strain; LBBB, Left Bundle Branch Block; LV, left ventricle; NYHA, New York

Heart Association functional class; SF, septal flash

Table 2. Comparative data on left ventricular size, function, and myocardial work in CRT-responders and non-responders at baseline and at 6-month follow-up

| | Responders | Non-responders | <i>p-value</i> |
|-------------------------------------|--------------------|-----------------------|----------------|
| | N=118 (71%) | N=48 (29%) | |
| <i>Baseline</i> | | | |
| LV-EDV, ml/m ² | 117±42 | 129±41 | 0.037 |
| LV-ESV, ml/m ² | 83±35 | 89±36 | 0.15 |
| LV-EF, % | 28±7 | 28±8 | 0.62 |
| LV-GLS, % | -9±3 | -7±3 | 0.0001 |
| Constructive work, mmHg% | 1104±434 | 838±324 | 0.0001 |
| Wasted work, mmHg% | 325±137 | 245±114 | 0.001 |
| <i>After 6 months of CRT</i> | | | |
| LV-EDV, ml/m ² | 80±28* | 129±38 | <0.0001 |
| LV-ESV, ml/m ² | 45±21* | 91±35† | <0.0001 |
| LV-EF, % | 45±11* | 28±9 | <0.0001 |
| LV-GLS, % | -13±4* | -8±4 | <0.0001 |
| Constructive work, mmHg% | 1452±420* | 920±372 | <0.0001 |
| Wasted work, mmHg% | 197±111* | 197±102† | 0.99 |

*p<0.0001 with respect to Baseline

†<0.05 with respect to Baseline

Table 3. Predictors of cardiac death at univariable and multivariable analysis. Two multivariate models were created: Model A not including CRT-reponse and Model B including CRT response

| | Univariable analysis | | | Multivariable analysis | | | | | |
|--------------------------------------|----------------------|--------------|----------|------------------------|--------------|----------|---------|-------------|----------|
| | HR | 95% CI | <i>p</i> | Model A | | | Model B | | |
| | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> |
| Age, <i>per year</i> | 1.08 | (1.01-1.15) | 0.02 | 1.07 | (1.00-1.14) | 0.05 | 1.07 | (1.00-1.15) | 0.04 |
| Male sex | 1.75 | (0.49-6.27) | 0.39 | | | | | | |
| Ischaemic disease | 3.99 | (1.34-11.94) | 0.01 | 2.99 | (0.79-11.16) | 0.10 | 2.33 | (0.71-1.15) | 0.16 |
| NYHA>2 | 1.39 | (0.46-4.24) | 0.56 | | | | | | |
| Arterial Hypertension | 0.81 | (0.22-2.95) | 0.75 | | | | | | |
| Diabetes | 2.56 | (0.69-9.45) | 0.16 | | | | | | |
| Dyslipidemia | 1.49 | (0.49-4.56) | 0.49 | | | | | | |
| Creatinine, <i>per μmol/L</i> | 1.01 | (0.99-1.93) | 0.07 | | | | | | |
| QRS duration, <i>per ms</i> | 0.99 | (0.97-1.03) | 0.81 | | | | | | |
| QRS>150 ms | 0.48 | (0.17-0.40) | 0.18 | | | | | | |
| LBBB | 0.87 | (0.27-2.77) | 0.81 | | | | | | |
| LVEF, <i>per %</i> | 0.99 | (0.92-1.08) | 0.89 | | | | | | |
| LVEDV, <i>per ml/m²</i> | 1.01 | (0.99-1.02) | 0.46 | | | | | | |
| LVESV, <i>per ml/m²</i> | 1.01 | (0.99-1.02) | 0.69 | | | | | | |
| Septal flash | 0.19 | (0.06-0.62) | 0.006 | 2.29 | (0.54-9.71) | 0.26 | 0.48 | (0.12-1.95) | 0.30 |
| LV-GLS | 1.21 | (0.99-1.47) | 0.06 | | | | | | |
| Wasted work, <i>per mmHg%</i> | 0.99 | (0.99-1.01) | 0.75 | | | | | | |
| Constructive Work, <i>per mmHg%*</i> | 0.99 | (0.99-1.00) | 0.04 | 0.99 | (0.99-1.01) | 0.03 | 0.99 | (0.99-1.00) | 0.04 |
| Constuctive Work ≤888 mmHg% | 4.76 | (1.33-17.12) | 0.01 | | | | | | |
| CRT-response** | 0.26 | (0.09-0.78) | 0.02 | | | | 0.68 | (0.18-2.57) | 0.58 |

CI, confidence interval; CRT-response, cardiac resynchronization therapy positive response;
HR, hazard ratio

*The continuous variable was inserted in the multivariate analysis

** CRT-response was added to multivariate analysis in Model B, but not in Model A.

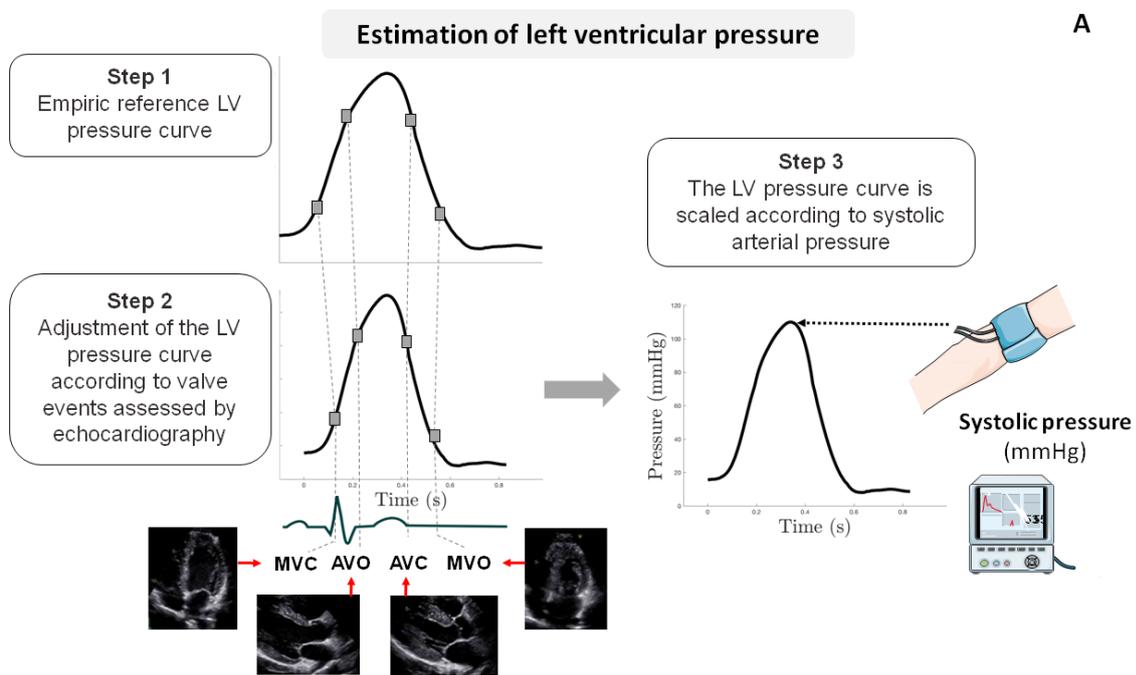
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Table 4. Incremental Prognostic Value of clinical parameters, CRT response, and myocardial constructive work: Discrimination Index Analysis

| | | Harrell's C-concordance |
|----------------|--------------------|-------------------------|
| Model 1 | Age | 0.73 |
| | Ischaemic disease | |
| Model 2 | Age | 0.75 |
| | Ischemic disease | |
| | Septal flash | |
| Model 3 | Age | 0.76 |
| | Ischemic disease | |
| | Septal flash | |
| | CRT response | |
| Model 4 | Age | 0.82 |
| | Ischemic disease | |
| | CRT response | |
| | Septal flash | |
| | CW \leq 888 mmHg | |

Figures

Figure 1A



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Figure 1B

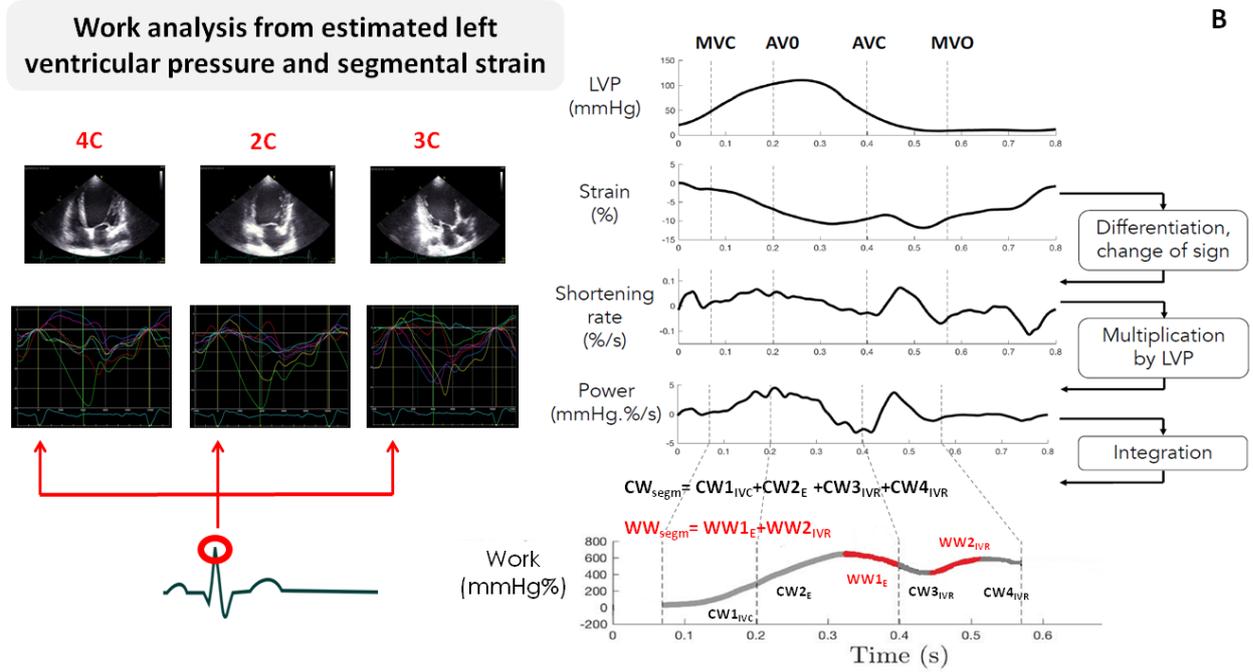
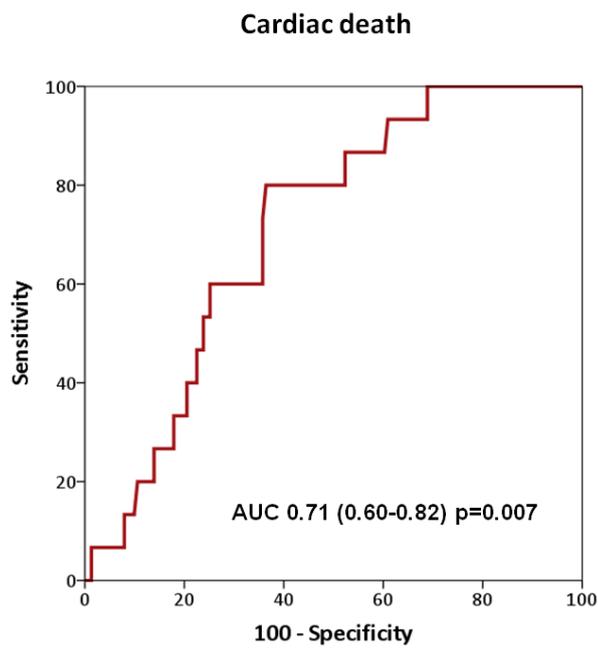
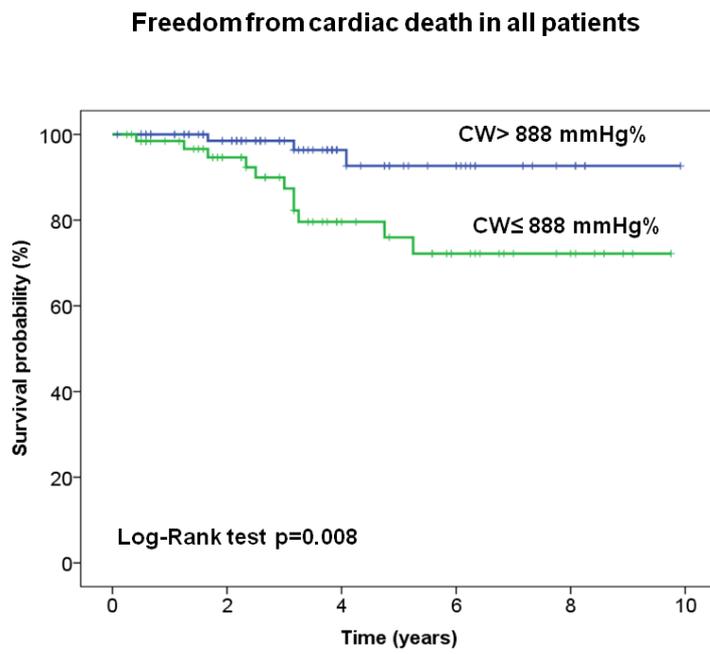


Figure 2



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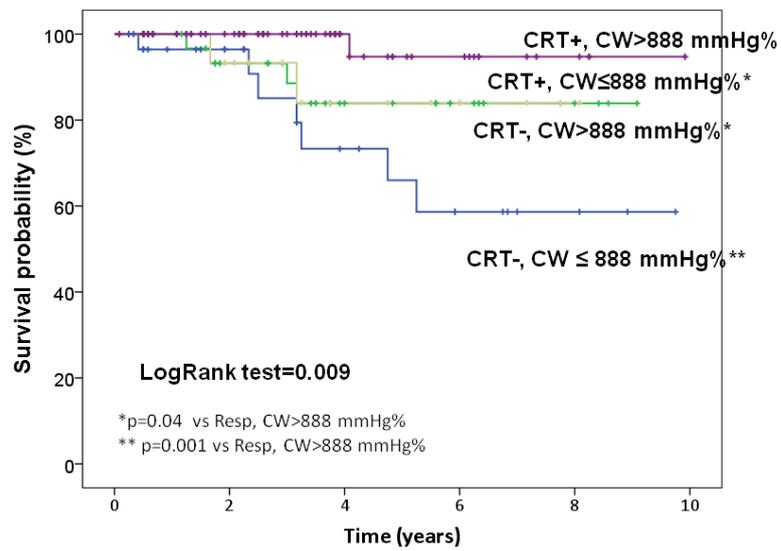
Figure 3



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Figure 4

Freedom from cardiac death according to CW and CRT response



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Figure 5

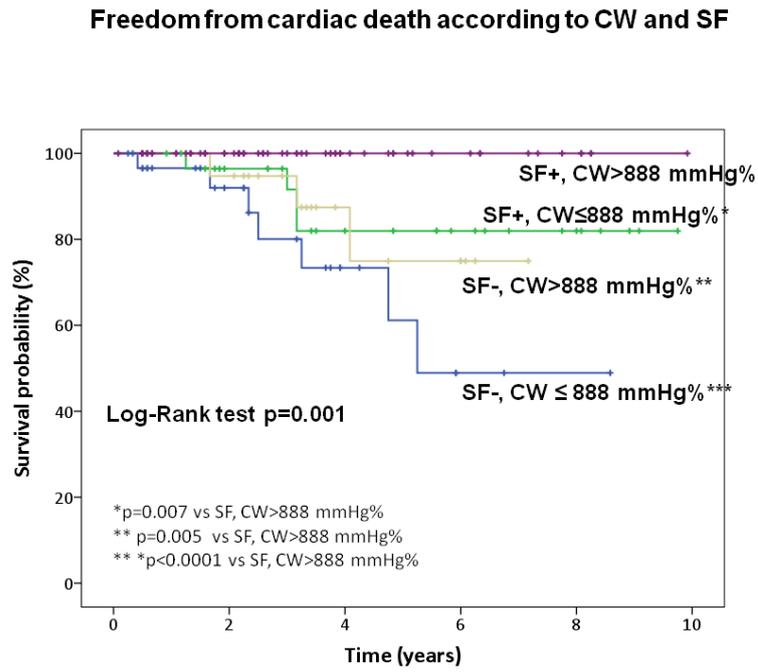
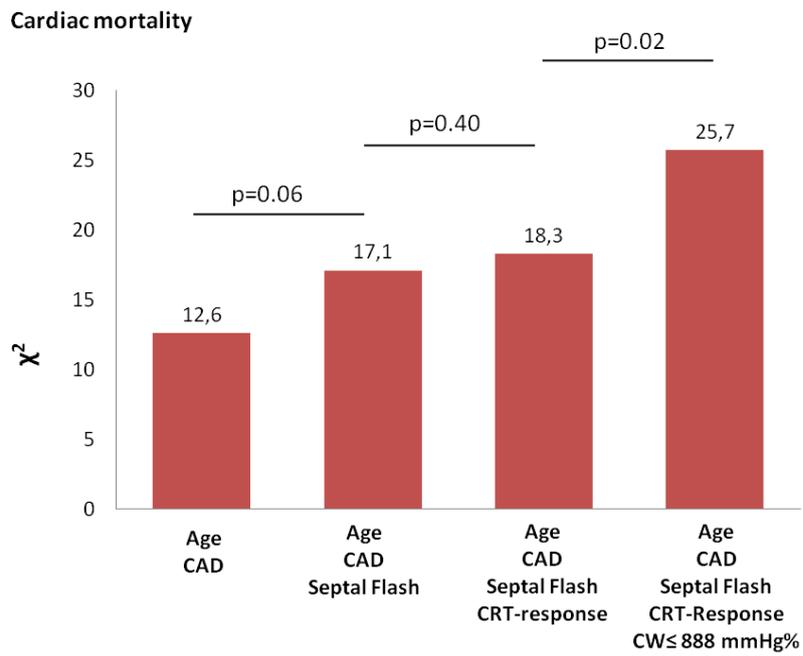


Figure 6



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