Prognostic Usefulness of Myocardial Work in Patients With Heart Failure and Reduced Ejection Fraction Treated by Sacubitril/Valsartan

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Running title: Myocardial work and Sacubitril/Valsartan

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Conflict of interest:

Prof. Erwan Donal got a research grant from Novartis France for this project.

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Highlights

- Sacubitril-Valsartan is a new treatment for heart failure with reduced ejection fraction which has a spectacular effect on survival
- The effect of this drug on myocardial work are unknown
- Sacubitril-Valsartan increases myocardial constructive work and work efficiency
- Pressure-strain loops are a recently introduced tool for the non invasive estimation of myocardial work.
- Constructive work a prognostic of major adverse cardiac events in patients with heart failure receiving Sacubitril-Valsartan

ABSTRACT

The non-invasive assessment of myocardial work (MW) by pressure-strain loops analysis (PSL) is a relative new tool for the evaluation of myocardial performance. Sacubitril/Valsartan is a treatment for heart failure with reduced ejection fraction (HFrEF) which has a spectacular effect on the reduction of cardiovascular events (MACEs). This study aimed to evaluate the short and medium term effect of Sacubitril/Valsartan treatment on MW parameters and the prognostic value of MW in this specific group of patients. 79 patients with HFrEF (mean age: 66±12 years; LV ejection fraction: 28±9%) were prospectively included in the study and treated with Sacubitril/Valsartan. Echocardiographic examination was performed at baseline, and after 6- and 12-month of therapy with Sacubitril/Valsartan.

Sacubitril/Valsartan significantly increased myocardial constructive work (CW) (1023±449 vs 1424±484 mmHg%, p<0.0001) and myocardial work efficiency (WE) [87 (78-90) vs 90 (86-95), p<0.0001]. During FU (2.6±0.9 years), MACEs occurred in 13 (16%) patients. After correction for LV size, LV ejection fraction and WE, global myocardial constructive work (CW) was the only predictor of MACEs [HR 0.99 (0.99-1.00), p=0.04]. A CW<910 mmHg identified patients at particularly increase risk of MACEs [HR 11.09 (1.45-98.94), p=0.002, log-rank test p<0.0001]. In conclusion, in patients with HFrEF who receive a comprehensive background beta-blocker and mineral-corticoid receptor antagonist therapy, Sacubitril/Valsartan induces a significant improvement of myocardial CW and WE. In this population, the estimation of CW before the initiation of Sacubitril/Valsartan allows the prediction of MACEs.

Keywords: Heart failure; Myocardial work; LV remodeling; Sacubitril/Valsartan

Introduction

Heart failure (HF) is a major public health problem due to its high prevalence, major morbidity and mortality[1]. Sacubitril/Valsartan, an inhibitor of the angiotensin receptor-neprilysin[2], has demonstrated a 20% relative reduction in cardiovascular death and a 16% relative risk reduction in all-cause mortality, when compared with Enalapril. This prognostic effect is associated with a striking improvement in left ventricular (LV) function and reverse remodelling[3], which could be attributed to the afterload reduction induced by this treatment[4]. Compared to LV ejection fraction (LVEF) and global longitudinal strain (GLS), which are largely affected by LV afterload[5,6], the assessment of myocardial work (MW) by pressure-strain loops analysis has the advantage to take into account the effect of LV afterload on myocardial performance[7,8]. The aims of this study were to 1) evaluate the short and medium-term effect of Sacubitril/Valsartan treatment on MW parameters in a prospective population of patients with HFrEF; 2) to evaluate the prognostic impact of MW on major adverse cardiovascular events (MACEs)

Methods

This is a prospective, observational, single-center study conducted at the University Hospital of Rennes from November 2015 to January 2018. Seventy-nine symptomatic patients with HFrEF and an indication to receive Sacubitril/Valsartan according to current recommendations[1] were prospectively and consecutively enrolled. Before the introduction of Sacubitril/Valsartan, all patients were receiving optimized medical therapy (OMT), which included adequate titration of diuretics to reduce the signs of congestion and achieve euvolemia. All patients were in sinus rhythm and had a good acoustic window allowing the assessment of MW. Patients with moderate or severe valvular heart disease were not included in the study. Clinical data, including age, gender, New York Heart Association (NYHA) functional class, systolic and diastolic blood pressure, medical therapy were assessed for each

patient before Sacubitril/Valsartan administration (baseline) and at 6- and 12-month follow-up (FU). Coronary artery disease (CAD) was defined as a history of myocardial infarction or coronary revascularization, or angiographic evidence of multiple-vessel disease or single-vessel disease with ≥75% stenosis of the left main or proximal left anterior descending artery. Trans-thoracic echocardiography was performed at baseline, 6- and 12-month FU. Data on the vital status of patients, hospitalization and ventricular arrhythmic events were collected from hospital medical records or by interview with the patient's general practitioner or relatives. The presence of ventricular arrhythmias (VAs) was defined by the occurrence of sustained ventricular tachycardia demanding hospitalization, or implantable cardioverter-defibrillator (ICD) appropriate choc. Major cardiac events (MACEs) were defined as the composite of cardiac death, heart failure-related hospitalization, and VAs.

The study was conducted following the "Good Clinical Practice" Guidelines in the Declaration of Helsinki. All patients provided written informed consent for participation in the study. The study protocol has been approved by the Ethical Committee (CCP Sud-Est V, N° ID RCB: 2017-A02217-46).

All patients were receiving the maximum tolerated HF treatment before Sacubitril/Valsartan initiation. This treatment included the maximum tolerated β-blockers, angiotensin converting enzyme inhibitors (ACEI) or sartan dosage. Diuretics were titrated to the appropriate dosage necessary to achieve euvolemia. The first Sacubitril/Valsartan dose was 24/26mg or 49/51mg twice daily according to blood pressure, age and biologic parameters. A washout period of 36 hours was respected before Sacubitril/Valsartan initiation in patients switching from an angiotensin-converting enzyme (ACE) inhibitor. Titration of Sacubitril/Valsartan treatment was left at the discretion of the physicians up to a target dosage of 97/103mg twice daily.

All patients underwent transthoracic 2D-echocardiography using standard equipment (Vivid 9 or 95, GE Healthcare, Horten, Norway) equipped with a 3S or M5S 3.5-mHz transducer before initiation of the Sacubitril/Valsartan therapy, at 6- and 12-month FU with the same imaging protocol. Bidimensional, colour Doppler, pulsed-wave and continuous-wave Doppler data were stored on a dedicated workstation for the offline analysis (EchoPAC, GEHealthcare, Horten, Norway).

Cardiac dimensions and function, especially LV and left atrial volumes, were measured according to current recommendations and LVEF was calculated using the Simpson biplane method[9].

Peak early (E) and late diastolic flow velocity (A), were measured from the apical 4-chamber view by pulsed-wave Doppler. Tissue Doppler imaging was used to assess peak early diastolic tissue velocity (e') at the lateral and septal mitral annulus. The average E/e' ratio was calculated to estimate LV filling pressure according to recommendations[10]. In patients with detectable tricuspid regurgitation, systolic pulmonary artery pressure (PAPs) was estimated using the maximal velocity of the tricuspid regurgitation jet (TRV_{max}) and an estimation of the right atrial pressure (RAP) based on the inferior vena cava size and collapsibility according to the following formula: $PAPs= 4x (TRV_{max})^2 + RAP$[11].

Two-dimensional grayscale images were acquired in the apical 4-, 3-, and 2-chamber views at a frame-rate of at least 60 frames/s. The recordings were processed off-line using an acoustic-tracking dedicated software (EchoPAC version 202, GE Healthcare, Horten, Norway) to estimate LV global longitudinal strain (GLS).

Myocardial work (MW) and related indices were estimated using a vendor-specific module (EchoPAC Version 202, GE Vingmed Ultrasound, Norway), by the combination of LV strain data and the non-invasive estimation of the LV pressure at cuff-arm sphygmomanometer as previously described[7,12].

An example of the estimation of MW parameters at baseline, 6-month, and 12-month after Sacubitril/Valsartan treatment is depicted in figure 1.

Normality of the distribution of continuous variables was tested by the Kolmogorov–Smirnov test. Normally distributed variables were expressed as mean±standard deviation (SD) and compared using the paired sample Student's *t*-test. Non-normally distributed variables were expressed as median and interquartile range (IQR) and compared using the Wilcoxon's test. Categorical data are expressed as numbers and percentages and compared by the χ^2 test.

Univariable Cox proportional hazards analysis of baseline clinical, electrocardiographic and echocardiographic characteristics was performed using MACEs as endpoints. 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. Receiver operator characteristics curve (ROC) analysis was used to determine a CW cutoff that was able to predict MACEs. Freedom from MACEs was plotted for both CW groups using Kaplan-Meier curves and between-group differences in freedom from events were tested using the log-rank test.

All statistical analyses were performed using Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA) and tests were 2-sided at the 0.05 significance level.

Results

Characteristics of patients at baseline, 6-month, 12-month FU are depicted in table 1. Sacubitril/Valsartan treatment was started at the dosage of 24/26 mg twice daily in 41(52%) patients, and at the dosage of 49/51 mg twice daily in 38 (48%) patients. The maximal dose of 97/103 mg twice daily was reached by 14 (17%) patients at 6-month and by 36 (46%) patients at 12-month follow-up. Only 2 patients (3%) discontinued Sacubitril/Valsartan before 12-month FU.

All patients had significant LV dilatation at baseline, and mean LVEF was 28±9%. After Sacubitril/Valsartan initiation, the main improvement in LV size and function was observed at 6-month FU. A modest improvement in diastolic function was evident at 6-month FU and persisted at 12-month FU (Table 1).

Myocardial work data at baseline, 6- and 12 month-FU are depicted in table 1.

CW increased significantly from baseline to 6-month FU. A modest, non significant improvement of CW was observed between 6- and 12-month FU. On the contrary, WW was not affected by Sacubitril/Valsartan treatment. A significant improvement in WE was observed only after 12-month of Sacubitril/Valsartan treatment. The effect of Sacubitril/Valsartan on myocardial work was similar in patients with and without ischemic cardiomyopathy. Noteworthy, in patients with coronary artery disease, the improvement in CW was delayed, becoming significant only at 12-month FU (Table 2).

The mean clinical FU was 2.6±0.9 years. During this period, MACEs occurred in 13 patients: 7 patients were hospitalized for HF recurrence, 2 patients died of refractory heart failure (1 died before 12 month-FU), and 4 patients had sustained VAs. In the univariable Cox-regression analysis, LV size, LVEF, GLS, CW, WE were all predictors of events. At multivariable regression analysis, CW was an independent predictor of MACEs (Table 3). An alternative model, including GLS instead of CW is provided in Table S1.

ROC curve analysis showed that a cutoff value of 910 mmHg% for CW was the best predictor of MACEs [AUC 0.81, 95% CI: 0 0.81 (0.69-0.94), p=0.0001, sensitivity 92%, specificity 67%] (Figure 2).

Kaplan-Meier survival curves (Figure 3) showed that CW≤910 mmHg% was highly associated with a poor outcome (log-rank p<0.0001). Patients with CW≤910 mmHg% had a higher risk of MACEs [HR 11.09 (1.45-98.94), p=0.002, log-rank test p<0.0001]).

Discussion

This is the first study to assess the additive effect of Sacubitril/Valsartan (on the top of optimal medical treatment) on MW parameters in patients with HFrEF and to show the prognostic role of MW in this specific group of patients.

Myocardial work estimation by PSL allows the non-invasive assessment of myocardial performance in a way that is non-invasive, reproducible and takes loading conditions into account, providing a better understanding of the pathophysiological mechanisms of HFrEF.

Chan et al. were the first to describe MW parameters in patients with dilated cardiomyopathy[13]. They found a significant decrease in CW and WE, and a rightward shift and reduction of the LV-PSL area, despite the presence of a preserved cardiac output. These alterations are also evident in our population, and underscore the fact that in patients with severely impaired LV systolic function, LV stroke volume can be maintained for a long time despite the alteration in LV contractility because of the significant increase in LV volumes.

Sacubitril/Valsartan induced a significant LV reverse remodeling, and a modest, but significant improvement in LV filling pressure, as witnessed by the progressive decrease in the E/e' ratio. A modest insignificant decrease in PAPs was also observed during follow-up. This data might seem in contrast with the improvement in filling pressure, but can be explained by the fact that maximal tricuspid regurgitation was measurable only in 35 and 51% of patients at 6- and 12-month FU. The overall improvement in patient's hemodynamic is also underscored by the small, but significant increase in systolic blood pressure observed at 12-month FU.

Sacubitril/Valsartan led to a significant improvement of CW which was already evident at 6-month FU, and to a delayed improvement in WE which became evident at 12-month FU with respect to baseline.

The improvement in CW can be attributed to the effect of Sacubitril/Valsartan on both LV wall stress[4] and myocardial perfusion[14]. The decrease in LV wall stress is confirmed in our population by the reduction in NTproBNP, a biomarker which is directly related to wall stress[4,15], and by the reduction in filling pressure, as supported by the progressive decrease of the E/e' ratio and LV volumes at 6-month FU.

Sacubitril/Valsartan has proven to increase myocardial perfusion and reduce fibrosis in the infarct "border zone"[14], through the significant reduction of the profibrotic signaling[16]. The strict relationship between wall stress and myocardial fibrosis, as far as the correlation between PSL and myocardial metabolism[7] might explain the positive effect of Sacubitril/Valsartan on LV remodeling and MW parameters in both ischemic and non-ischemic patients.

Despite the relationship between myocardial work and interstitial fibrosis is a matter of debate, the relationship between CW and replacement fibrosis has already been described in patient with hypertrophic cardiomyopathy[17]. We can hypothesize that the anti-fibrotic effect of Sacubitril/Valsartan might diminish myocardial stiffness, improve myocardial perfusion and metabolism, and facilitates myocytes' shortening during systole and relaxation during the early diastolic phase, which can contribute to the improvement of myocardial performance and CW.

In our study, Sacubitril/Valsartan had only a modest effect on WW. This observation might be explained by the fact that WW levels were only mildly elevated in our population, and nearer to the upper normality limit observed in healthy subjects[18]. WW seems more influenced by LV discoordination, as observed in patients with left bundle branch block, that by intrinsic LV contractility[17,19,20]. The net results of this progressive improvement of CW during Sacubitril/Valsartan treatment, without significant modification in WW is a delayed improvement in WE, which was reached at 12-month FU.

Sacubitril/Valsartan treatment has shown a spectacular prognostic impact on patients with HFrEF, by the significant reduction of both cardiovascular and overall-mortality[2,21].

The prognostic impact of CW has already been shown in patients with HFrEF undergoing CRT[12]. In our population, baseline CW emerged as a significant predictor of MACEs. Patients with CW≤910 mmHg had particularly advanced disease, greater LV end-diastolic (118±45 vs 95±34 ml/m^2, p=0.01) and end-systolic (92±39 vs 65±27 ml/m^2, p=0.001) volumes and more impaired LVEF (23±7 vs 32 ±8%, p<0.0001) at baseline.

These conditions might be associated with a reduced myocardial metabolism and increased LV stiffness and fibrosis, and therefore explain the dismal prognosis and increased number of ventricular arrhythmias observed in this subgroup[22].

This is a monocentric prospective study realized on a limited number of patients with HFrEF. The number of events observed was also limited, which can largely influence the results we obtained. 75% of included patients were males, which might prevent the application of our results to women with HF receiving Sacubitril/Valsartan. Patients with atrial fibrillation were excluded, which prevents the application of our results to a great proportion of patients with HF. Myocardial viability, scarring, interstitial or replacement fibrosis by cardiac MRI or nuclear imaging were not investigated in the current study. Such investigations may be important to further understand the relationship between CW, fibrosis and LV remodelling in patients treated by Sacubitril/Valsartan. The non-invasive estimation of myocardial work by pressure-strain loops rely upon the use of brachial cuff pressure to estimate LV pressure. This approach may not accurately replicate the LV hemodynamic profile during LV ejection and be a source of errors in the calculation of myocardial work. Moreover, myocardial work might be relatively underestimated in the dilated ventricles in which there is higher wall stress at any given LV pressure compared to smaller ventricles.

CW assessed by PSLs is a recently introduced parameter that can predict long-term outcome in patients with HFrEF receiving Sacubitril/Valsartan. CW≤910 mmHg identifies a subgroup of patients with a significantly dismal prognosis. Further studies on larger population are needed to confirm our results and allow their application in clinical practice..

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Figure legends

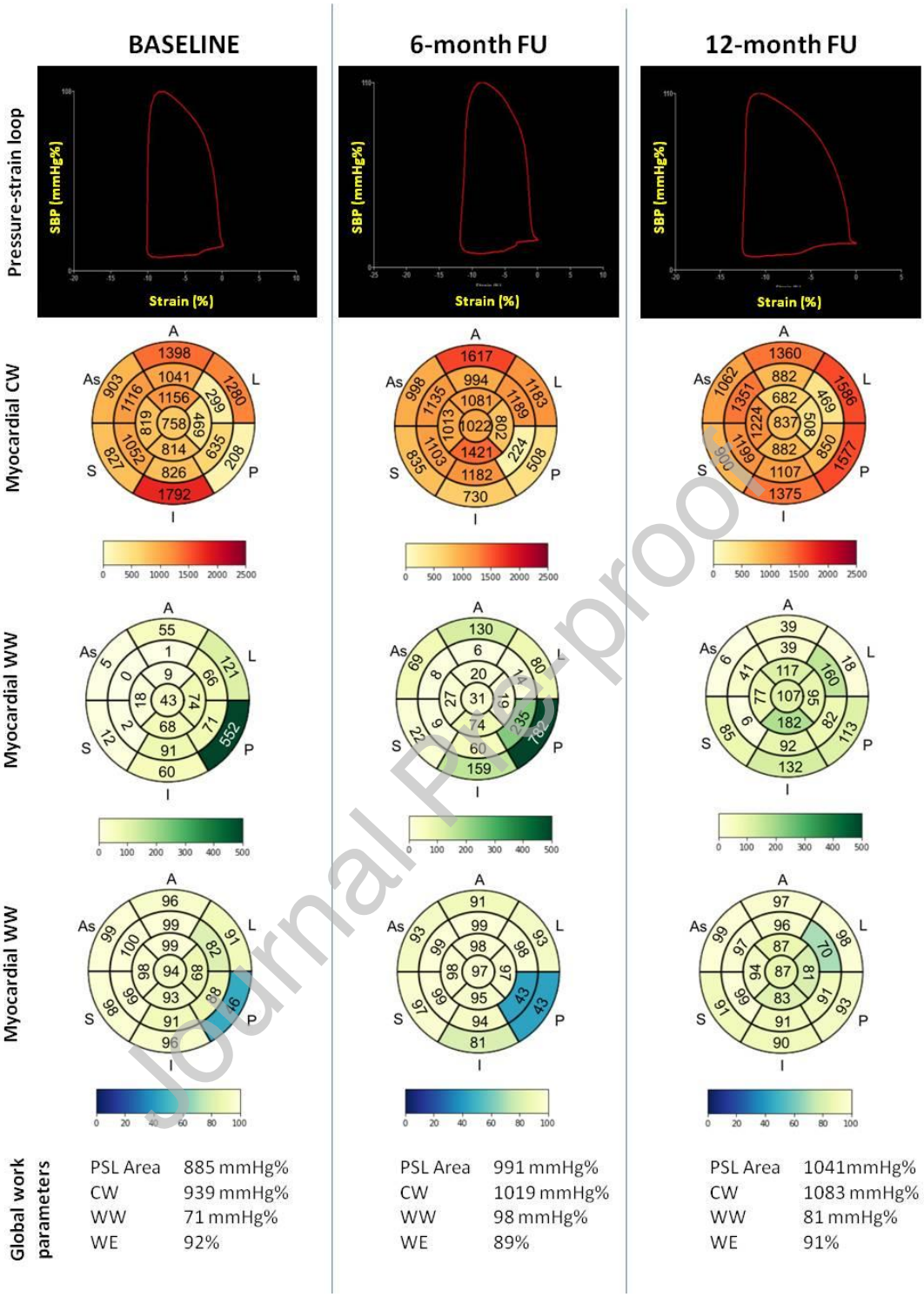

Figure 1. Example of the assessment of myocardial work parameters by pressure strain-loop analysis at baseline and at 6- and 12- month follow-up

CW, constructive work; PSL, pressure-strain loop; SBP, systolic blood pressure; WE, work efficiency; WW, wasted work.

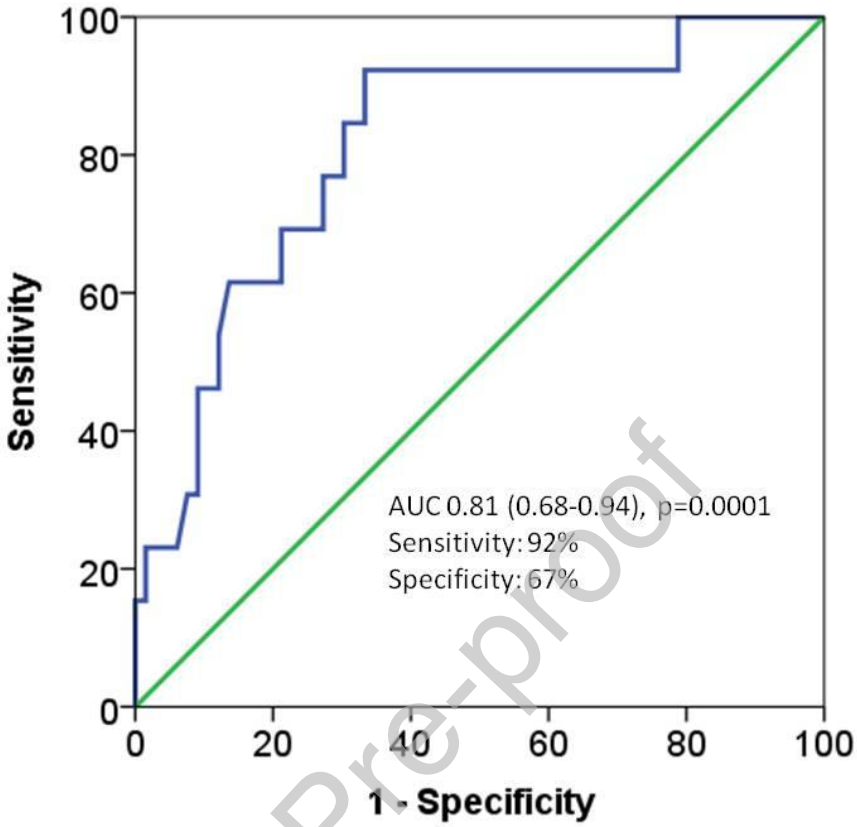

Figure 2. Receiving operator characteristic curve analysis of left ventricular constructive work (baseline value) for the prediction of major adverse cardiac events

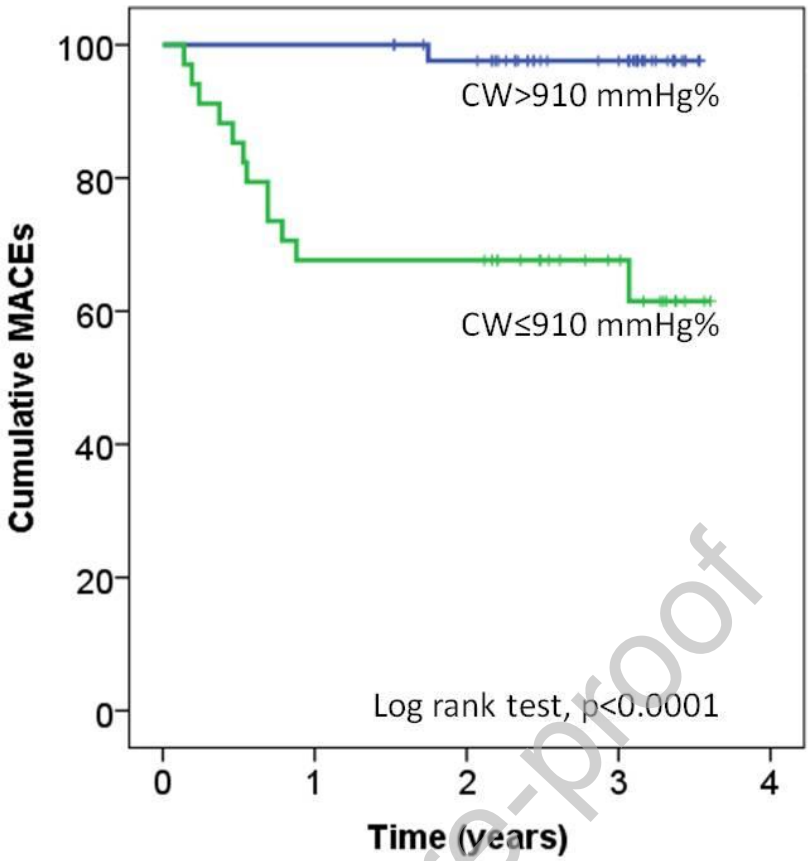

Figure 3. Kaplan-Meier estimates of the time to major cardiac adverse events displayed according to the presence of CW≤ 910 mmHg% or CW>910 mmHg% at baseline.

CW, constructive work

AUTHOR CONTRIBUTION STATEMENT

Yanis Bouali	Collection of data; conceptualization; analysis of data; writing and editing the paper;
Erwan Donal	Reviewing the paper; supervision of the research activity
Clement Laurin	Collection of data; analysis of data
Alban Gallard	Writing and editing the paper, creation of figures
Arnaud Hubert	Writing and editing the paper
Auriane Bidaut	Writing and editing the paper
Christophe Leclercq	Reviewing the paper supervision of the research activity
Elena Galli	Conceptualization; Validation of data; Analysis of data; Writing, reviewing and editing the paper; supervision of the research activity

Table 1. Clinical and echocardiographic data at baseline, 6-month, and 12-month follow-up

Variable	Basal (N=79)	6-month FU (N=79)	12-month FU (N=78)
Age (years)	67 (59-76)	-	-
Men	59 (75%)	-	-
Coronary artery disease	38 (48%)	-	-
NYHA class	2.2±0.6	1.8±0.5*	1.7±0.6*
Congestion	29 (37%)	7 (9%)*	9 (12%)*
LnNTproBNP (ng/l)	6.9±0.9	6.3±1.1*	6.4±1.3*
Systolic blood pressure (mmHg)	120±16	121±18	127±20†
Diastolic blood pressure (mmHg)	71±12	70±11	70±13
β-blockers	74 (94%)	61 (77%)*	61 (78%)*
Aldosterone antagonists	42 (53%)	28 (35%)*	36 (46%)
ACE-Inhibitors/Sartans	79 (100%)	1 (1%)*	2 (3%)*
Diuretics	53 (67%)	37 (47%)*	39 (50%)*
Sacubitril/Valsartan discontinuation		1 (1%)	2 (3%)
Sacubitril/Valsartan dosage			
24/26 (mg)	41 (52%)	15 (19%)	9 (12%)
49/51 (mg)	38 (48%)	50 (63%)	33 (42%)
97/103 (mg)	-	14 (17%)	36 (46%)
Indexed left ventricular end-diastolic volume (ml/m^2)	105±40	94±39*	93±37*
Indexed left ventricular end-diastolic volume (ml/m^2)	77±35	61±34*	58±32*
Cardiac output (L/min)	3.7±1.2	4±1.5	4.1±1.1
Left ventricular ejection fraction (mm)	28±9	37±11*	40±12*,†
Global longitudinal strain(%)	-9 (-6-11)	-10 (-6-13)*	-13 (-9-16)*
Indexed left atrial volume (ml/m^2)	40 (32-55)	42 (28-62)	41 (33-56)
E-wave (cm/sec)	87 (60-100)	76 (53-90)	78 (50-99)
E/e'	13 (10-22)	12 (9-15)*	11 (9-15)*
Systolic pulmonary artery pressure (mmHg)	44±11	43±21	38±19
Myocardial constructive work (mmHg%)	1023±449	1269±520*	1424±484*
Myocardial wasted work (mmHg%)	110 (78-184)	140 (82-238)	112 (77-178)
Myocardial work efficiency (mmHg%)	87 (78-90)	87 (80-90)	90 (86-95)*

†<0.05 vs 6-FU; *≤0.01 vs basal assessment

Table 2. Comparison of myocardial work parameters in ischemic and non-ischemic patients at baseline and during follow-up

Variable	Patients with coronary	Patients without	*p-value*

	artery disease	coronary artery disease	
Myocardial constructive work at baseline (mmHg%)	994±446	1045 ±407	0.58
Myocardial constructive work at 6-month follow-up (mmHg%)	1112±445	1409±549*	0.02
Myocardial constructive work at 12-month follow-up (mmHg%)	1301±493*	1534±455*	0.14
Myocardial wasted work at baseline (mmHg%)	138 (83-212)	107 (76-165)	0.36
Myocardial wasted work at 6-month follow-up (mmHg%)	153 (70-242)	125 (89-245)	0.98
Myocardial wasted work at 12-month follow-up (mmHg%)	104 (78-181)	126 (76-176)	0.74
Myocardial work efficiency at baseline (%)	84 (75-89)	87 (83-91)	0.06
Myocardial work efficiency at 6-month follow-up (%)	86 (75-90)	88 (83-93)	0.25
Myocardial work efficiency at 12-month FU WW (%)	89 (83-94)*	90 (87-95)*	0.29

* p<0.001 vs basal

Table 3. Predictors of major adverse cardiac events at Cox regression analysis

Variable	***Univariable analysis***		***Multivariable analysis***	
	HR (95% CI)	***p-value***	**HR (95% CI)**	***p-value***
Age (per year)	0.99 (0.95-1.04)	0.81		
Coronary artery disease	1.07 (0.36-3.21)	0.89		
Indexed left ventricular end-diastolic volume (per ml/m^2*)	1.01 (1.00-1.03)	0.03		
Indexed left ventricular end-diastolic volume (per ml/m^2)	1.01 (1.00-1.03)	0.009	1.01 (0.99-1.02)	0.35
Left ventricular ejection fraction (per %)	0.91 (0.85-0.98)	0.01	1.02 (0.93-1.12)	0.71
Global longitudinal strain (per %)**	1.16 (1.00-1.35)	0.05		
E/e’	1.04 (0.98-1.11)	0.15		
Myocardial constructive work (per mmHg%)	0.99 (0.99-1.00)	0.002	0.99 (0.99-1.00)	0.04
Myocardial wasted work (per mmHg%)	1.00 (0.99-1.01)	0.22		
Myocardial work efficiency (per mmHg%)	0.91 (0.86-0.96)	0.001	0.95 (0.88-1.02)	0.16

*This variable was not inserted in the multivariable model because showing significant collinearity with indexed left ventricular end-systolic volume.

**This variable was not inserted in the multivariable model because showing significant collinearity with myocardial constructive work.