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Association of ventricular–arterial interaction with the response to cardiac resynchronization therapy

Deterioration in endothelial function can discriminate chronic heart failure (CHF) patients in terms of functional status and prognosis, as it has been related to disease progression, increase in hospitalizations and mortality.[1,2] Markers of endothelial dysfunction (ED) and arterial stiffness include flow-mediated dilatation (FMD), carotid to femoral pulse wave velocity (cfPWV) and the layer of endothelial glycocalyx.[3] Assessment of ventricular–arterial coupling (VAC) and interaction can be performed non-invasively via echocardiography using the arterial elastance (Ea) to ventricular elastance (Ees) ratio (Ea/Ees) and the most recent cfPWV to global longitudinal strain (GLS) of the left ventricle ratio (cfPWV/GLS).[4,5] Cardiac resynchronization therapy (CRT) in patients with reduced ejection fraction (EF) and electrical dyssynchrony has demonstrated improvement in quality of life, CHF symptoms, exercise capacity and mortality reduction but its effect in ED and arterial stiffness has not been thoroughly investigated.[1–3,6,7] Reduced nitric oxide, cytokines, oxidative stress proteins and growth factors ascending from ED worsen myocardial microcirculatory function and arterial vasoreactivity.[1,3,4] An upturn in endothelial function and arterial elastic properties could promote response to therapy, clinically and echocardiographically, by reduction in left ventricular end-systolic volume (LVESV).[3–5] In this study, we sought to evaluate the effect of CRT on VAC, ED, peripheral vascular function, and their associated markers, but also to determine among them predictors of response to CRT.

Thirty-two consecutive CHF patients with conventional indications for CRT were prospectively evaluated before and 3 months after CRT implantation in accordance with previous studies.[1,8] Informed consents were obtained from all patients. The study fulfilled the Declaration of Helsinki and was approved by the ethics committee of the institution.

In each visit we performed a 12-lead electrocardiogram and evaluated vascular function via cfPWV and FMD. We assessed LVEF, left ventricular GLS and analysed the Ea/Ees ratio by echocardiography and the cfPWV/GLS ratio, as valid markers of ventricular–arterial interaction. Left ventricular diameters and volumes were measured and LVEF was conducted using Simpson's method. Patients that demonstrated a reduction in LVESV more than 15% compared to baseline were defined as responders. Ea and Ees were estimated using the simplified formula Ea = end-systolic pressure/stroke volume, Ees = end-systolic pressure/end-systolic volume. Left ventricular GLS was quantified using two-dimensional speckle tracking echocardiography from the apical long-axis, two- and four-chamber views. Originating from the negative GLS value, the cfPWV/GLS ratio presented negative value: the more negative the value, the less abnormal. FMD analysis was performed by a blinded investigator according to specific recommendations. We also measured endothelial glycocalyx by measuring perfused boundary region (PBR) of the sublingual microvessel range: 5–25 μm (higher PBR indicates lower endothelial glycocalyx thickness). Studies were performed after CRT programming and optimization.

The primary endpoint was a change in ventricular–arterial interaction, by calculation of the Ea/Ees and cfPWV /GLS ratios, as well as changes in ED and arterial stiffness, as assessed by FMD, cfPWV and PBR 5–25, 3 months after CRT implantation. We also assessed baseline markers mentioned above as possible predictors of response to CRT as secondary endpoint. A standard chi-square test was applied to examine the categorical variables and a *t*-test (or paired *t*-test) was used to compare differences in mean values of continuous variables. Linear regression was used to investigate relations between improvement in LVEF, GLS, Ea/Ees, cfPWV/GLS, cfPWV, PBR 5–25, and FMD with changes in LVESV. The accuracy of baseline parameters or their changes in predicting response to CRT was estimated using receiver operating characteristic (ROC) curves analysis.

The reported odds ratios (OR) by logistic regression analysis were adjusted for age, sex and type of cardiomyopathy (ischaemic vs. non-ischaemic cardiomyopathy). Internal validation was performed via bootstrapping and 95% confidence interval (CI) of the area under the curve and coordinates of best (or optimal) thresholds for each parameter were estimated using 10 000 stratified bootstrap replicates. Based upon previous studies regarding the effect of CRT on vascular function[1,8] with an alpha of 5% and power of 80%, we required a sample of 26 patients to detect significant changes in the examined markers after CRT and 14 CRT responders to detect differences between responders and non-responders.

Thirty-two patients with a mean age 65.5 (±10.9) years and severe left ventricular dysfunction (baseline LVEF: 27 ± 7%, LVESV: 151 ± 42 mL, GLS: −6.47 ± 2.89%) were followed up for a median of 115 days (interquartile range 36, Q1 97, Q3 133) (*Table 1*). Twenty-three were male and 15 suffered from ischaemic heart disease, none of our patients suffered from aortic valve disease. QRS duration was reduced after CRT compared with baseline (158 ± 26 vs. 142 ± 21 ms, $P = 0.029$). During follow-up, LVEF and GLS were significantly increased (mean change: 7.50 ± 4.77% and 2.85 ± 2.28%, respectively) and LVESV was significantly reduced (mean change: −26.91 ± 17.20 mL). All measurements of endothelial function exhibited significant change: FMD increased by 4.37 ± 3.34% ($P < 0.001$), PBR 5–25 decreased by 0.13 ± 0.25 μm ($P = 0.028$), while Ea/Ees decreased by 0.77 ± 0.47% ($P < 0.001$) and cfPWV by 1.10 ± 1.56 ($P = 0.003$). Twenty-three of 32 patients were classified as responders (LVESV change >15% compared to baseline). There were no differences in baseline values of myocardial and vascular markers between CRT responders and non-responders ($P > 0.05$ for all comparisons). Non-responders were more likely to have ischaemic cardiomyopathy (7/9), and to be male (9/9).

Among the examined baseline markers, only the baseline cfPWV/GLS ratio predicted response to CRT (OR 0.245, 95% CI 0.042–0.759, $P = 0.044$). Threshold analysis

Table 1 General characteristics of the study population according to echocardiographic response to cardiac resynchronization therapy

	All patients ($n = 32$)	Responders ($n = 23$)	Non-responders ($n = 9$)
Age (years)	65.5 ± 10.9	66.6 ± 10.9	63.8 ± 9.6
Male sex	23	14	9
Ischaemic	15	8	7
Atrial fibrillation	3	3	0
LBBB	30	23	7
Non-LBBB	2	0	2
QRS duration (ms)	158 ± 26	161 ± 25	156 ± 21
NYHA functional class	2.7 ± 0.5	2.6 ± 0.6	2.8 ± 0.6
LVEF (%)	27 ± 7	28.1 ± 7	26.8 ± 9
LVESV (mL)	151 ± 42	141 ± 43	152 ± 60
SBP (mmHg)	126 ± 19	124 ± 14	127 ± 27
DBP (mmHg)	79 ± 19	80 ± 10	77 ± 7

DBP, diastolic blood pressure; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; SBP, systolic blood pressure.

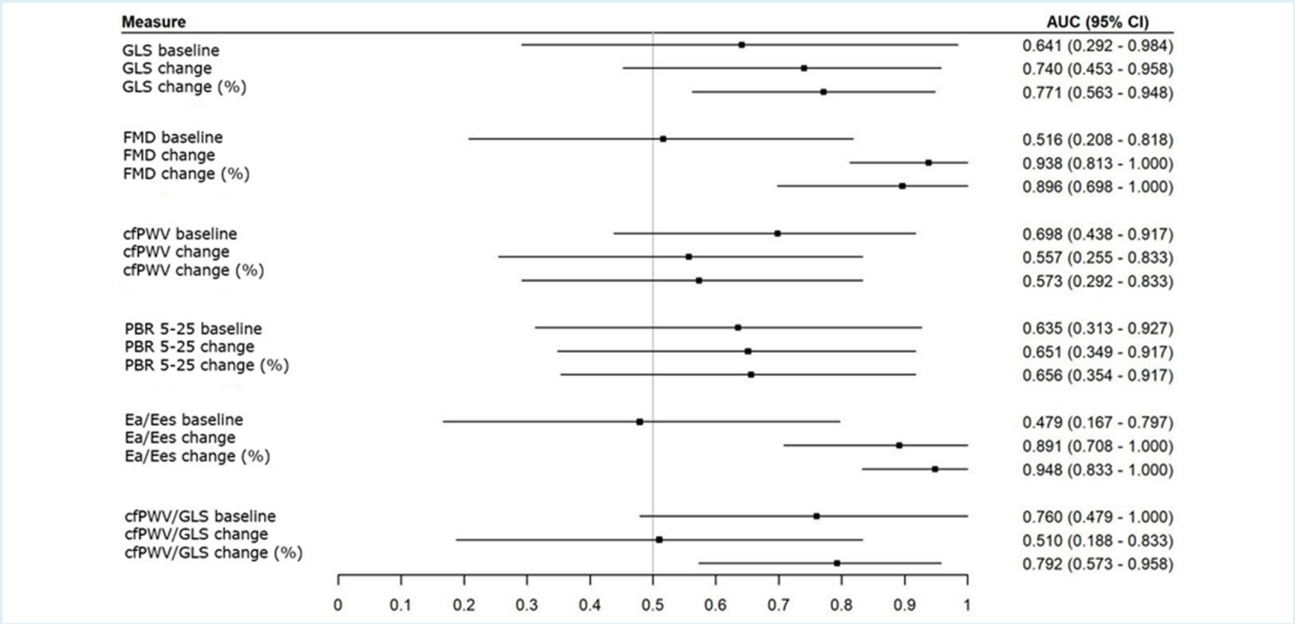

Figure 1 Predictive power of measurements at baseline and their change during follow-up for response to cardiac resynchronization therapy [based on the area under the receiver operating characteristic curves (AUC)]. The 95% confidence intervals (CI) were estimated based on 10 000 stratified bootstrap replicates. cfPWV, carotid to femoral pulse wave velocity; Ea/Ees, arterial elastance to ventricular elastance ratio; FMD, flow-mediated vasodilatation; GLS, global longitudinal strain; PBR, perfused boundary region.

by ROC showed that the best threshold of cfPWV/GLS was −2.75 (specificity: 67%, sensitivity: 94%) for response to CRT (*Figure 1*). Among the changes of the examined markers during follow-up, CRT response associated with the change of FMD (OR 3.10, 95% CI 1.47–15.51, $P = 0.039$) and standardized Ea/Ees change (OR 0.021, 95% CI 0.000–0.267, $P = 0.0239$).

In our study, CRT implantation significantly improved endothelial function, arterial elasticity and ventricular–arterial interaction. However, response to CRT was most evident when the interaction between vascular and myocardial function was improved, as response to CRT was better predicted by the respective changes of Ea/Ees. This pinpoints the beneficial impact of CRT in the entire circuit compiled by the left ventricle, aortic valve, ascending aorta and peripheral vessels.[4]

To our knowledge, this is the first study to provide preliminary data for combined use of ED and VAC markers in stratification of CRT response. It highlights the component of the arterial load: many patients who fulfil conventional CRT criteria do not necessarily benefit from this expensive device therapy, some of them even deteriorate further.[6,7] Over the past years, several non-invasive indices have been examined in stratification of CRT response. Despite initial promising

results in single centre trials, such indices have failed to distinguish themselves in larger trials. A main reason of this phenomenon is that these indices present high inter-observer variability and ultimately fail to dissociate accurately responders and non-responders to CRT before implantation.[6,7]

Our study presented limitations. Patients' sample was tight, factors influencing CRT response such as presence of scar and lead placement were not assessed and response criterion was based solely upon LVESV reduction. A limitation of the use of echocardiography to determine VAC is that the volume–axis intercept is assumed to be negligible in comparison to LVESV.[4] Still, in our study, response to CRT rate was in concordance with larger randomized trials and patients' characteristics resemble most closely daily practice.[6,7]

Our work suggests that measurement of VAC markers such as Ea/Ees or cfPWV/GLS in addition to standard CRT implantation criteria may provide incremental benefit and these findings should be evaluated in larger randomized studies.

Conflict of interest: none declared.

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The CLIP-based mortality score in cardiogenic shock: suitable only for cardiogenic shock?

We read with interest the article by Ceglarek *et al.*[1] recently published in the *European Heart Journal*. The authors described, from a prospective cohort including 458 patients admitted for cardiogenic shock (CS) complicating acute myocardial infarction (AMI), a new routinely available biomarker-based risk score called CLIP score [acronym of cystatin C, lactate, interleukin-6 and N-terminal pro B-type natriuretic peptide (NT-proBNP) dosed at admission] for 30-day mortality prediction in CS patients. Internally (from the CULPRIT-SHOCK trial) and externally validated (from the IABP-SHOCK II trial), the CLIP score was developed to improve early risk stratification of patients admitted for CS secondary to AMI, and it includes the prognostically most important biomarkers selected by a penalized multivariable logistic regression technique (Least Absolute Shrinkage and Selection Operator, LASSO). The CLIP score yielded a c-statistics for 30-day mortality of 0.82 [95% confidence interval (CI) 0.78–0.86] in internal (n = 458), 0.82 (95% CI 0.75–0.89) in internal-external validation (n = 152) and 0.73 (95% CI 0.65–0.81) in external validation (n = 163). According to the authors, the main interest of this score is that each biomarker explores a complex part of the pathophysiology of CS related to AMI (lactate for global tissue hypoxaemia, NT-proBNP as a marker of cardiac wall stress in congestive heart failure, interleukin-6 as a proinflammatory cytokine, and cystatin C as a parameter of renal function and potential inflammatory biomarker), thus explaining the rationale for using the CLIP score in CS related to AMI. Despite existing risk stratification scores (with clinical and biological items) in CS, namely the CardShock[2] and IABP-SHOCK II scores,[3] the authors developed this new score.

FROG-ICU (French and European Outcome Registry in Intensive Care Unit, NCT01367093) is an international, multicentre, observational cohort study previously described[4] including consecutive patients admitted to intensive care unit (ICU) for severe diseases, mainly CS, septic shock, haemorrhagic shock and acute respiratory failure, and followed up during 1 year after hospital discharge. The study was conducted in accordance with Good Clinical Practice and Helsinki Declaration, and Ethics Committee approval (Comité de Protection des Personnes – IRB n. 00003835 and IRB n. B403201213352) was obtained as per the French law.[5] Patients were included from August 2011 to June 2013. By applying the formula given by Ceglarek *et al.* based on the dosage of cystatin C, lactate, interleukin-6 and NT-proBNP at inclusion, we aimed to test the ability of the CLIP score to predict the 30-day mortality from main causes of ICU admission by calculating the area under the curve (AUC) of receiver operating characteristic analysis (ROC). Comparisons of AUC were assessed using DeLong's method. In addition, we assessed the 30-day mortality probability according to CLIP score values at inclusion, for each cause of admission. Continuous variables were expressed as median and interquartile range (IQR). Categorical variables were expressed as counts and percentages. A P-value < 0.05 was considered statistically significant.

In conclusion, the CLIP score is an easy, reliable and reproductive score During the study period, 2087 patients, mainly men (n = 1361, 65%), with a median age of 63 (IQR 51–74) years, were included for CS (n = 146, 7%), septic shock (n = 488, 23%), haemorrhagic shock (n = 110, 5%) and acute respiratory failure (n = 394, 19%). Other causes of ICU admission were cardiac arrest (n = 179, 8.6%), traumatic brain injury (n = 286, 13.7%), post-operative management (n = 207, 9.9%), traumatism (n = 89, 4.3%), liver (n = 25, 1.2%) and kidney failure (n = 17,