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ORIGINAL PAPER

The mechanistic interaction between mechanical dyssynchrony and filling pressure in cardiac resynchronisation therapy candidates

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Aims Both left ventricular (LV) mechanical dyssynchrony and filling pressure have been shown to be associated with outcome in heart failure patient treated with cardiac resynchronisation therapy (CRT). To investigate the mechanistic link between mechanical dyssynchrony and filling pressure and to assess their combined prognostic value in CRT candidates.

Methods and results Left atrial pressure (LAP) estimation and quantification of mechanical dyssynchrony were retrospectively performed in 219 CRT patients using echocardiography. LAP was elevated (eLAP) in 49% of the population, normal (nLAP) in 40%, and indeterminate in 11%. CRT response was defined as per cent-decrease in LV end-systolic volume after 12 ± 6 months CRT. Clinical endpoint was all-cause mortality during 4.8 years (interquartile range: 2.7–6.0 years). To investigate the mechanistic link between mechanical dyssynchrony and filling pressure, the CircAdapt computer model was used to simulate cardiac mechanics and haemodynamics in virtual hearts with left bundle branch block (LBBB) and various causes of increased filling pressure. Patients with nLAP had more significant mechanical dyssynchrony than those with eLAP. The combined assessment of both parameters before CRT was significantly associated with reverse LV remodelling and post-CRT survival. Simulations revealed that mechanical dyssynchrony is attenuated by increased LV operational chamber stiffness, regardless of whether it is caused by passive or active factors, explaining the link between mechanical dyssynchrony and filling pressure.

Conclusion Our combined clinical-computational data demonstrate that in patients with LBBB, the presence of mechanical dyssynchrony indicates relatively normal LV compliance and low filling pressure, which may explain their strong association with positive outcomes after CRT.

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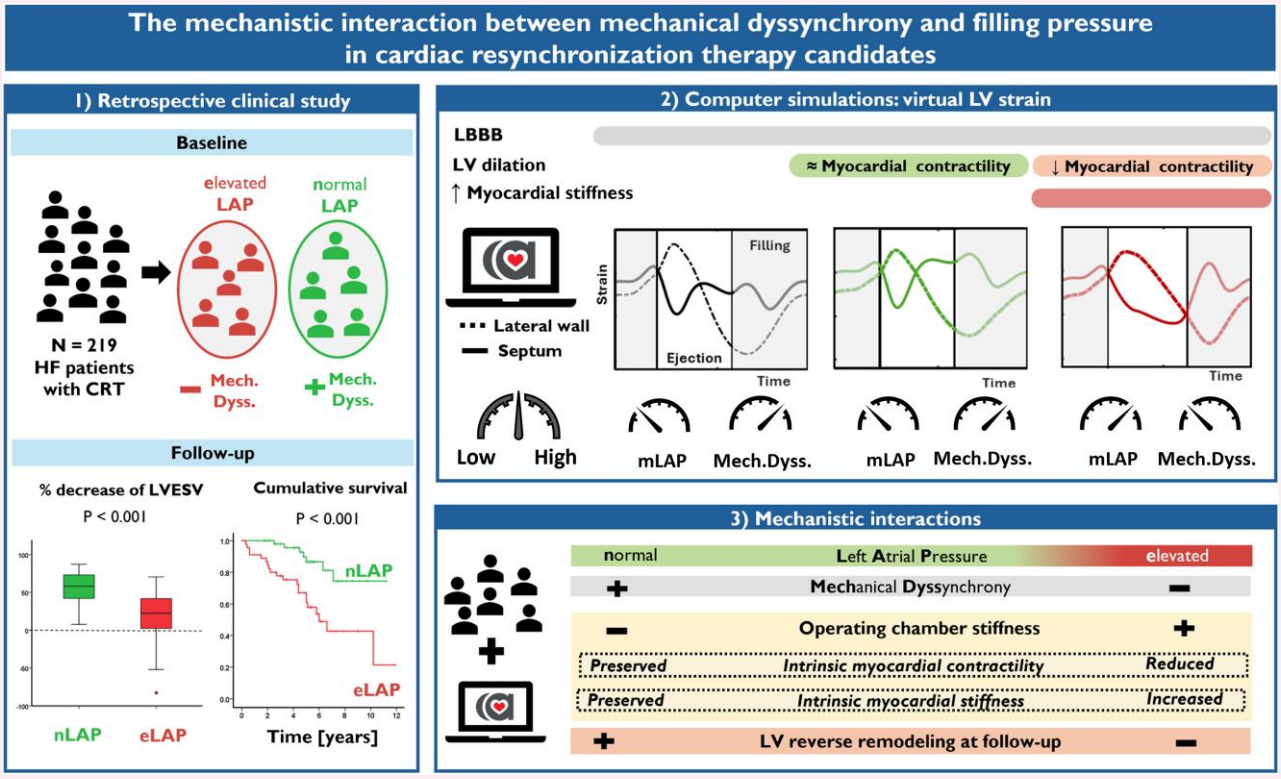
Graphical Abstract



The present study combining clinical data and computer simulations shows that in heart failure patients receiving cardiac resynchronisation therapy (CRT), clearly observed mechanical dyssynchrony (Mech.Dyss.) is associated with lower operating chamber stiffness and normal (*n*) left atrial pressure (LAP). Alternatively, higher operating chamber stiffness either due to reduced contractility or to increased intrinsic myocardial stiffness leads to both elevated (e) LAP as well as less evident Mech.Dyss. Clinical data indicate that the joint echocardiography-based assessment of Mech.Dyss. and LAP before CRT holds substantial prognostic significance. LVESV, left ventricular end-systolic volume; mLAP, mean LAP.

Keywords diastolic function • contractility • compliance • speckle tracking • heart failure • substrate

Introduction

Cardiac resynchronisation therapy (CRT) has been shown to be an effective treatment for patients with heart failure with reduced ejection fraction and ventricular conduction delay.[1] Despite its established efficacy, the heterogeneous response to CRT has triggered extensive research aimed at identifying predictors for favourable outcomes. Among others, mechanical dyssynchrony and estimated left atrial pressure (LAP) have emerged as predictors of CRT outcome.[2–8] Despite their recognized individual prognostic value, their mechanistic interplay in CRT patients remains unexplored.

In 2016, the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) introduced a multi-parametric echocardiography-based algorithm for non-invasive estimation of LAP (LAP).[9] The proposed algorithm has been validated in various cardiac pathologies, including left bundle branch block (LBBB).[10] Recent studies revealed associations between nLAP and positive CRT outcomes, such as reverse left ventricular (LV) remodelling and enhanced post-CRT survival.[7,8]

Many studies have shown rather strong associations between the novel echocardiography-based indices of mechanical dyssynchrony and CRT outcome. Although these indices are practically different, they assess the same septal-to-lateral mechanical interaction, which is known to reflect both the electrical activation delay caused by LBBB and the underlying mechanical properties of the LV myocardium.[2–6]

In the present study on heart failure patients treated with CRT, we aim at exploring the association between mechanical dyssynchrony and estimated LAP, both assessed using echocardiography. We additionally investigate the impact of combined baseline assessment of both parameters on reverse LV remodelling and long-term patient's survival. Furthermore, we used the multi-scale CircAdapt model of the human heart and circulation[11,12] to elucidate the mechanistic interaction between estimated LAP and mechanical dyssynchrony in virtual CRT candidates with various types of LV dilatation characterized by impaired myocardial contractility and compliance.

Methods

Clinical data

Study population

We retrospectively investigated 219 CRT patients from the database of Jessa Hospital (Hasselt, Belgium). Patient selection was based on the availability of complete sets of data including patient characteristics,

comorbidities, heart failure medication, electrocardiogram (ECG), and echocardiography before CRT implantation and during follow-up as well as survival data. We excluded 17 patients from further analysis due to bad quality of baseline echocardiography. All patients were on optimal medical therapy for heart failure for at least 3 months prior to CRT. Ischaemic cardiomyopathy (ICM) was defined based on coronary angiography data or on records of myocardial infarction. The study was approved by the Ethics Review Committee of Jessa Hospital (study number: 2023-019).

CRT implantation

All patients received CRT (76% with a defibrillator). Guided by coronary venography, LV pacing leads were preferably positioned in the lateral or posterolateral coronary venous branches.

Electrocardiography

All patients had 12-lead surface ECG before CRT, which was digitally stored and analysed offline using SEMA data management system (SCHILLER medical systems) for identification of rhythm, QRS width and morphology. LBBB was defined based on the criteria proposed by the 2013 European Society of Cardiology Guidelines on cardiac pacing and CRT.[13]

Echocardiography

All echocardiographic examinations were done using the commercially available Vivid S6 and E9 ultrasound systems (GE Healthcare, Horten, Norway). All images were digitally stored and analysed offline using the EchoPac software version 204 (GE medical systems, Horten, Norway). All patients had transthoracic echocardiography examination at 2 ± 3 months before CRT. During each echocardiographic examination LV volumes and ejection fraction (LVEF) were measured using the biplane Simpson's method of disks. LV speckle tracking strain analysis was performed at baseline on the three apical views view. The quality of tracking was visually checked and manually adjusted where needed following the expert consensus recommendations.[14]

Diastolic function analysis

A full transthoracic echocardiography-based LV diastolic function analysis was performed on all patients at baseline. Mitral inflow pulsed wave Doppler was used to estimate peak E-wave velocity, E-wave deceleration time (E-DT), peak A-wave velocity and duration, and E/A-ratio. Isovolumic relaxation time (IVRT) was measured as the time between aortic valve closure and mitral valve (MV) opening using continuous wave (CW) Doppler. Tissue Doppler imaging was applied to septal and lateral side of the MV annulus where septal and lateral e′ velocities were respectively recorded, and the average value of both was calculated. Tricuspid regurgitation peak velocity (TR-Vmax) was estimated using CW Doppler whenever feasible. Left atrium volume indexed to body surface area (LAVi) was estimated using the biplane method of disks.

Non-invasive estimation of LAP

LAP was estimated at baseline using the multi-parametric guideline algorithm proposed by the 2016 ASE/EACVI Guideline.[9] In patients with more than moderate mitral regurgitation (MR) as well as patients with atrial fibrillation (AF) at the time of image acquisition (total $n = 22$), additional echocardiographic parameters were used to estimate LAP, including IVRT and pulmonary venous flow analysis following the recommendations of the guidelines.[9] Patients were classified into three groups based on the estimated LAP category: normal (nLAP), elevated (eLAP) and, in a subgroup of patients, indeterminant (iLAP), where LAP could not be determined. This was due to the unavailability of necessary echocardiographic indices, resulting from technical issues such as sub-optimal image quality or inadequate Doppler signals.

Assessment of mechanical dyssynchrony

In the present work, mechanical dyssynchrony was assessed using echocardiography and was initially defined as the presence of apical rocking and/or septal flash (ApRock/SF) in 2D B mode.[3] Given its relative feasibility and reproducibility in clinical setting, ApRock/SF was used as the main index for differentiating between patients with and without mechanical dyssynchrony. Additionally, mechanical dyssynchrony was fully quantified using the systolic stretch index (SSI),[5] and the difference between lateral and septal myocardial work [lateral wall (LW)-S work difference].[6] *Figure 1* shows the main indices used for the assessment of mechanical dyssynchrony in the study. Furthermore, mechanical dyssynchrony was assessed using septal strain patterns (1 = double peak, 2 = dominant stretch after initial shortening, and 3 = pseudonormal shortening)[2] and the global wasted work (GWW) index.[15] To maintain clarity and avoid adding complexity to the main text, the detailed analysis of these two indices was provided in the Supplementary material.

CRT outcome

Functional response to CRT was defined as the percentage decrease of LV end-systolic volume (LVESV) at 12 ± 6 months after CRT compared with baseline. Additionally, all patients were followed-up for all-cause mortality for a mean duration of 4.8 years [interquartile range (IQR): 2.7–6.0 years].

Model simulations

The CircAdapt model of the human cardiovascular system enables real-time and realistic simulation of beat-to-beat mechanics and haemodynamics in the cardiac chambers, the pulmonary circulation, and the systemic circulation. It is configured as a closed-loop network of modules representing myocardial walls, cardiac valves, large blood vessels, and peripheral resistances (see Supplementary data online, *Figure S1*). It simulates physiological signals, such as blood pressures in the cardiac chambers and large blood vessels, blood flow through valves, and local myofiber mechanics in the cardiac walls. The active and passive behaviour of the myocardium is described by 3-element Hill-type contraction model. The CircAdapt model incorporates mechanical ventricular interaction through the interventricular septum as well as haemodynamic ventricular interaction through the systemic and pulmonary circulations. More details on the CircAdapt model description and validation can be found elsewhere.[11,12,16]

Modelling various types of virtual CRT candidates

To investigate the mechanistic interaction between mechanical dyssynchrony and mean LAP (mLAP), used as measure of filling pressure, we simulated five virtual CRT candidates with varying combinations of LV dilatation and myocardial stiffness (*Figure 2*). The reference model simulation represents a healthy cardiovascular system under baseline resting conditions (cardiac output = 4.1 L/min, heart rate = 65 bpm, and mean arterial pressure = 92 mmHg) with normal conduction and synchronous mechanical activation of the ventricular walls. During all simulations, the homeostatic pressure-flow regulation was kept activated so that mean arterial pressure and cardiac output are maintained at their resting values through changes in both systemic vascular resistance and total blood volume.

Simulation of LBBB electrical substrate

Like in previous studies,[2,17] LBBB was simulated by delaying the onset time of septal and left ventricular free wall (LVFW) mechanical activation with respect to the right ventricle-free wall (0–25 ms septum and 0–75 ms LVFW) without changing any of the tissue properties thus assuming no LV remodelling ('Simulation [1] LBBB + non-remodelled LV [normal contractility and compliance]', *Figure 2* and Supplementary data online, *Figure S1B*).

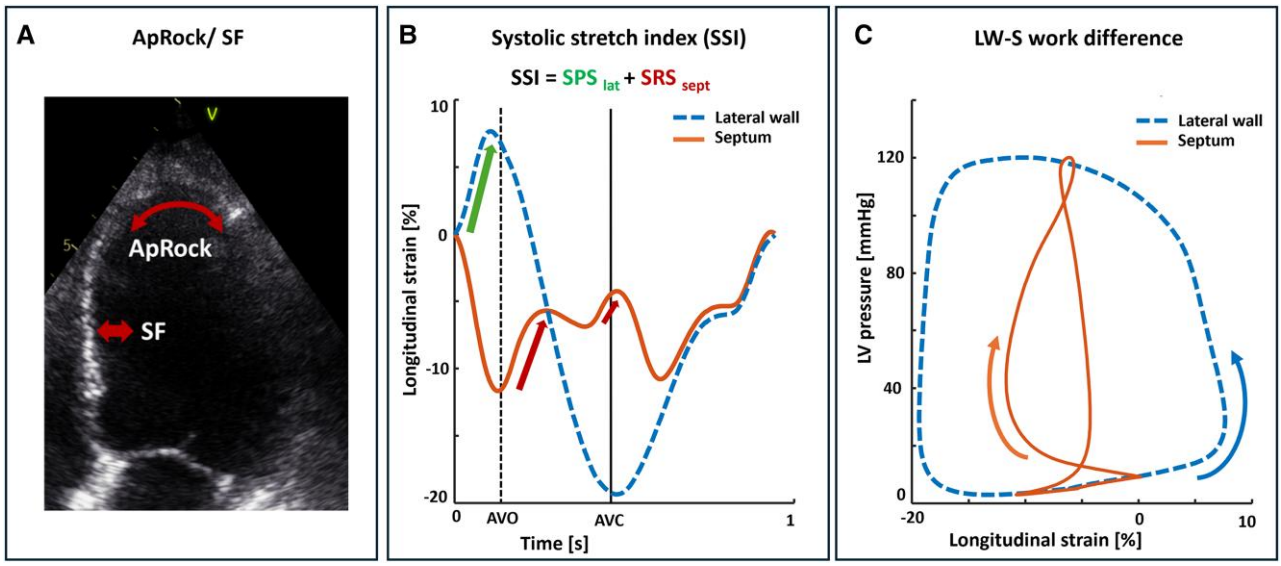


Figure 1 The different ECG-based indices of mechanical dyssynchrony assessment used in our study; (*A*) shows a still 2D image of the assessment of ApRock and SF (see Supplementary data online, *Video S1* 1); (*B*) shows the assessment of systolic stretch index (SSI) in a patient with LBBB which is the sum of the systolic pre-stretch of the lateral wall (SPS_{lat}) and the systolic rebound stretch of the septum (SRS_{sept}); (*C*) shows pressure-strain loops of the septum (S), and lateral wall (LW) of a patient with LBBB. The loop area represents the myocardial work where the LW–S work difference is the absolute difference in work values, calculated with the strain of each wall averaged over its mid- and basal-segments in the 4CH view. AVO, aortic valve opening; AVC, aortic valve closure.

Simulating LV remodelling

In addition to the LBBB electrical substrate, a typical CRT candidate would show an advanced stage of LV dilatation with an LVEF ≤ 35%.[18] We simulated two types of LV dilatation, both with an LVEF ≤ 35%, yet, with different tissue characteristics leading to normal or elevated filling pressure:

LV dilatation with normal filling pressure. A low value LVEF with normal filling pressure was simulated by increasing the cardiac wall mass and area, so that the ratio between the total LV wall volume, i.e. LVFW wall volume + septal wall volume, and the cavity volume is maintained.[19] Wall area and wall mass were increased to 135 and 145% of their reference values, respectively to obtain LVEF lower than 35% ['simulation (2), LBBB + LV dilatation with preserved contractility']. At tissue level, operating sarcomere length and, hence, contractile strength and passive tissue behaviour do not change. At organ level, LV end-diastolic volume (LVEDV) increases while filling pressure remains normal (*Figure 2* and Supplementary data online, *Figure S1C*).

LV dilatation with elevated filling pressure. In the model, we used two approaches to increase the filling pressure: (i) by decreasing contractility of the septum and in the LVFW through decreasing the isometric active myofiber stress, and (ii) by simulating diastolic dysfunction through increasing LV myocardial passive stiffness.

(1) Decreasing contractility. Here the force generated by the sarcomere was reduced at any sarcomere length. Accordingly, sarcomeres are forced to operate at larger length to develop sufficient contractile force. At organ level, this will lead to a decrease in LVEF with an increase of both LVEDV and filling pressure. Contractility was decreased to 70% of the reference value to reach LVEF below 35% ['simulation (3) LBBB + LV dilatation with reduced contractility', *Figure 2* and Supplementary data online, *Figure S1D* panel 3].
(2) Increasing passive stiffness. Here, the passive stiffness exponent that represents the passive myofiber stress arising from the extracellular matrix was increased. In case of reduced contractility (simulation 3), the tissue already operates at a stiffer part of the myocardial stress–strain relationship, thereby causing an increase of filling pressure. Therefore, a mild increase of the passive stress exponent is enough to reach a higher filling pressure. However, in the case of preserved contractility (simulation 2), the tissue is still viable; hence, a larger increase in stiffness is needed to obtain an increase in filling pressure comparable to the simulation of reduced contractility. Accordingly, we increased the passive stress exponent to 140% of the reference value in case of reduced contractility ('simulation 4, LBBB + LV dilatation with reduced contractility + increased stiffness', *Figure 2* and Supplementary data online, *Figure S1D* panel 4), whereas, for the preserved contractility, it was increased to 270% ('simulation 5, LBBB + LV dilatation with reduced contractility + increased stiffness', *Figure 2* and Supplementary data online, *Figure S1D* panel 5).

Myofiber strain and calculating indices of mechanical dyssynchrony in the model

Myofiber strain was calculated for both the septum and lateral free wall in the following way:

$$\varepsilon(t) = \left(\frac{Ls(t)}{Ls,\ ref} - 1\right)100\%.$$

$\varepsilon(t)$ refers to engineering strain and it is expressed as the fractional change in $Ls(t)$ of an elementary myocardial segment along its long axis during the cardiac cycle. Where Ls, ref is the sarcomere length at the chosen reference time (MV closure).

Similar to clinical measurements, SSI and LW-S work difference were calculated in every combination of simulations following the same methodology as in clinical measurements to show the influence of reduced myocardial contractility as well as increased myocardial stiffness on mechanical dyssynchrony.

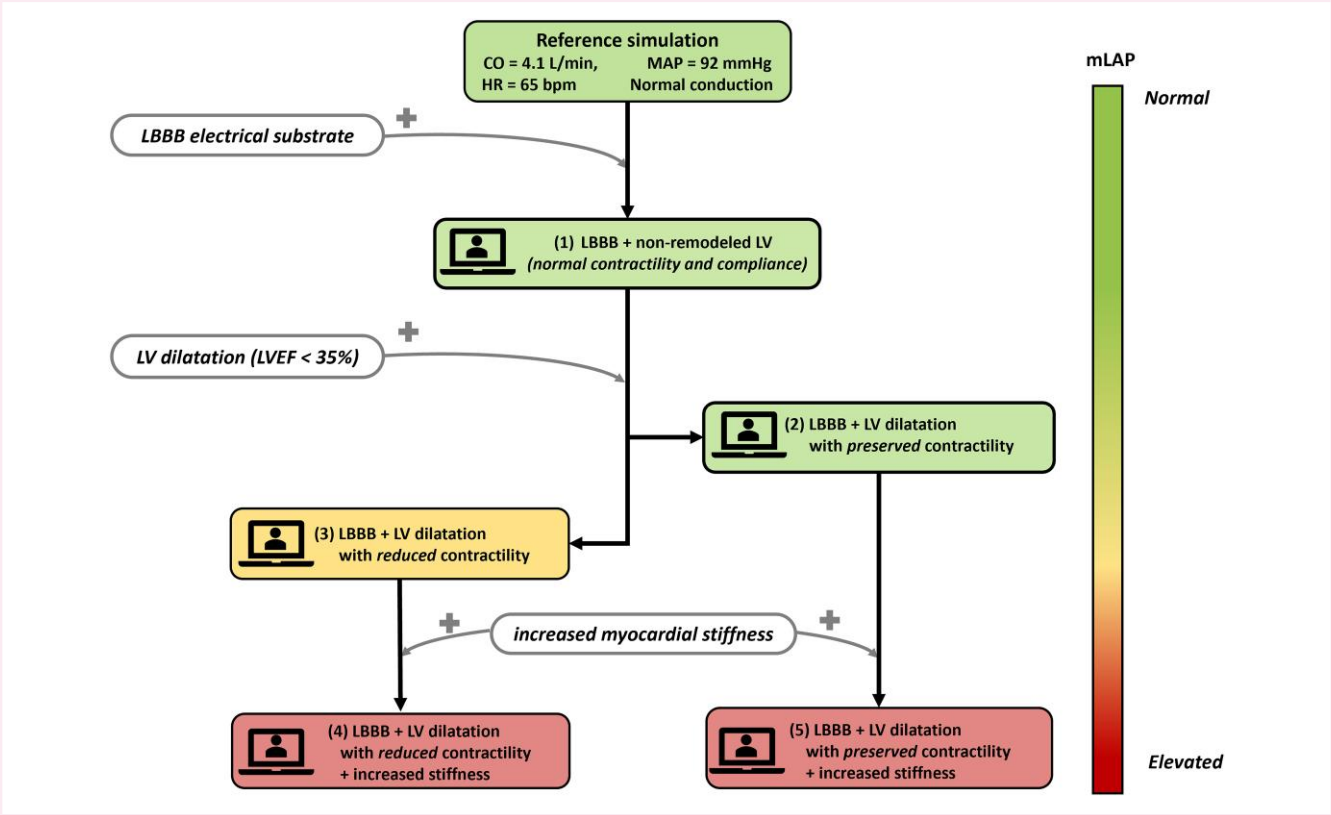


Figure 2 Schematic representation of the computer simulations of the five virtual CRT candidates along with an indication of their mLAP. Starting from baseline normal condition, step one is inducing LBBB [simulation (1)]. Step 2 is simulating two types of LV dilatation with LVEF < 35%; (i) with preserved contractility [simulation (2)] and (ii) reduced contractility [simulation (3)]. Step 3 is increasing intrinsic myocardial stiffness in both simulations of LV dilatation [simulations (4) and (5)]. Note that simulations (1) and (2) were associated with normal mLAP, while simulations (3–5)] were associated with elevated mLAP. CO, cardiac output; HR, heart rate.

Myocardial work density was defined as the area within the fibre stress-strain loop and can be interpreted as the regional equivalent of global stroke work.

End-diastolic elastance calculation

As previously described, end diastolic elastance (Eed), which represents the operational stiffness, was determined by measuring the tangent of the LV diastolic pressure–volume relationship at the end-diastole in various preload conditions.[20,21] Supplementary data online, *Figure S2* illustrates the end-diastolic pressure volume relationship for each simulation.

Statistical analysis

The normality of clinical data distribution was assessed using the Shapiro–Wilk test. For normally distributed data, the *t*-test was employed to compare continuous variables, and the results were presented as mean ± SD. For categorical variables, the χ^2 test was used, and data were expressed as percentages. In case of non-normal distribution, the Mann–Whitney *U* test or the Kruskal–Wallis test was employed to compare data between groups and results were presented as median and IQR. Survival rates were expressed using Kaplan–Meier's curves, while the significance of differences in survival rates between groups was compared using a Log-rank test. Cox-proportional hazard model was used to determine predictors of survival, while linear regression model was used to determine predictors of relative change of LVESV at follow-up. In both models, all relevant baseline variables were first tested separately in a univariate analysis and then tested all together in a multi-variable model to determine variable/s with an independent association with the outcome. The following variables were tested in both regression models: age at CRT implantation, gender, ICM, QRS duration, LBBB, AF, the use of angiotensin-converting enzyme inhibitors, the use of B-blockers, serum creatinine, diabetes mellitus (DM), LVEF, nLAP, and ApRock/SF. Data analysis were performed using SPSS (IBM Corp. released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA: IBM Corp.). Two-sided *P* value of < 0.05 was considered significant.

Results

Clinical patient data

Baseline characteristics of the study population.

Baseline characteristics of the study population stratified by the presence or absence of ApRock/SF are shown in *Table 1*. Patients with ApRock/SF were more of female sex; they had less ICM and a lower prevalence of DM. They had lower serum creatinine, and their use of renin angiotensin system inhibitors was more frequent than in patients without ApRock/SF.

Baseline ECG showed that patients with ApRock/SF had on average wider QRS complex with more LBBB-like morphology. Echocardiographic data showed that all echocardiographic indices of diastolic function were significantly better in patients with ApRock/SF except for the average e′. LV volumes and LVEF were similar in both groups.

Patients with LBBB pattern on ECG showed significantly higher prevalence of ApRock/SF ($P < 0.001$) as well as septal patterns 1 or 2

Table 1 Baseline characteristics of the study population

	+ApRock/SF ($n = 113$)	−ApRock/SF ($n = 89$)	*P* value
Demographics and comorbidities			
Age at implantation (years) (m ± SD)	70 ± 9	68 ± 12	0.228
Male sex, *n* (%)	68 (60%)	74 (83%)	**<0.001**
ICM, *n* (%)	47 (42%)	56 (63%)	**0.001**
NYHA-class (m ± SD)	2.7 ± 0.5	2.8 ± 0.5	0.097
DM, *n* (%)	21 (19%)	27 (30%)	**0.019**
Serum Hb (mg/dL) (m ± SD)	12.9 ± 1.8	12.7 ± 2.0	0.345
Serum creatinine (mg/dL) (m ± SD)	1.2 ± 0.5	1.4 ± 0.7	**0.001**
Heart failure medications			
ACEi, *n* (%)	98 (87%)	63 (71%)	**0.042**
BB, *n* (%)	98 (87%)	68 (76%)	0.264
Diuretics, *n* (%)	71 (63%)	61 (69%)	0.118
ECG data			
AF, *n* (%)	10 (9%)	14 (16%)	0.088
QRS (ms) (m ± SD)	159 ± 28	149 ± 26	**0.007**
LBBB, *n* (%)	69 (61%)	35 (39%)	**<0.001**
Echocardiographic data			
E-velocity (m/s) (m ± SD)	0.7 ± 0.3	0.8 ± 0.3	**<0.001**
E-DT (ms) (m ± SD)	219 ± 80	193 ± 87	**0.035**
A velocity (m/s) (m ± SD)	0.8 ± 0.3	0.6 ± 0.4	**<0.001**
E/A ratio (m ± SD)	1.2 ± 1.9	2.2 ± 4.1	**0.046**
Average e′, (m ± SD)	0.05 ± 0.01	0.05 ± 0.02	0.721
Average *E*/e′ (m ± SD)	16 ± 8	20 ± 11	**0.047**
TR-VMAX (m/s)	2.6 ± 0.6	2.8 ± 0.5	**0.042**
LAVi (mL/kg/m^2)	34 ± 15	42 ± 19	**0.015**
LVEDV (mL) (m ± SD)	172 ± 84	170 ± 70	0.821
LVESV (mL) (m ± SD)	120 ± 72	114 ± 56	0.480
LVEF (%) (m ± SD)	32 ± 10	33 ± 10	0.220

Baseline characteristics of the study population stratified by the presence (+) or absence (−) of ApRock/SF. The results are expressed as m ± SD for continuous variables and number (and percentage) for categorical variables. *P*-values of statistical significance (<0.05) are highlighted in bold.
ACEi, angiotensin-converting enzyme inhibitors; BB, B-blockers; Hb, haemoglobin; LA, left atrium; NYHA, New York Heart Association.

($P = 0.004$). Similarly, values of SSI were higher in patients with LBBB compared with patients without ($P = 0.042$). While LW-S work difference values did not differ significantly between both groups ($P = 0.067$), GWW values were higher in patients with LBBB compared with patients without ($P = 0.047$, Supplementary data online, *Table S1*).

The agreement between different indices of mechanical dyssynchrony

In 12% of the study population, the echocardiographic image quality was sub-optimal for strain analysis, while ApRock/SF was available in 100% of the study population.

Patients with ApRock/SF showed significantly higher values of SSI [4.9%, IQR: (2.8–7.8) vs. 1.6%, IQR: (0.4–3.2), $P < 0.001$] and LW-S work difference (671 ± 598 vs. 237 ± 487 mmHg%, $P < 0.001$) compared with patients with no ApRock/SF. Similarly, ApRock/SF was significantly associated with septal strain patterns 1 or 2 ($P < 0.001$) as well as with higher values of GWW ($P = 0.001$, Supplementary data online, *Figure S3*).

The association between mechanical dyssynchrony and estimated LAP in CRT candidates

None of the following cardiac conditions, which could complicate the guideline-based estimation of LAP, were present in our study population: significant mitral stenosis, significant aortic stenosis or regurgitation, mechanical heart valves, cardiac transplantation, non-cardiac pulmonary hypertension, constrictive pericarditis, restrictive cardiomyopathy, or hypertrophic cardiomyopathy. The distribution of LAP category in the study population was as follows, 40% with nLAP, 49% with eLAP, and 11% with iLAP. The distribution of missing diastolic indices in the sub-group of patients with iLAP is shown in Supplementary data online, *Figure S4*.

The prevalence of nLAP was significantly higher in patients with ApRock/SF compared with patients with no ApRock/SF (60 vs. 28%, $P < 0.001$, *Figure 3A*). Regarding fully quantifiable indices of mechanical dyssynchrony, patients with nLAP showed significantly higher value of SSI [4.0%, IQR: (2.1–7.8) vs. 2.8%, IQR: (0.7 ± 4.8), $P = 0.002$, *Figure 3B*], and LW-S work difference (662 ± 500 vs. 340 ± 300 mmHg%, $P = 0.011$) compared with patients with eLAP,

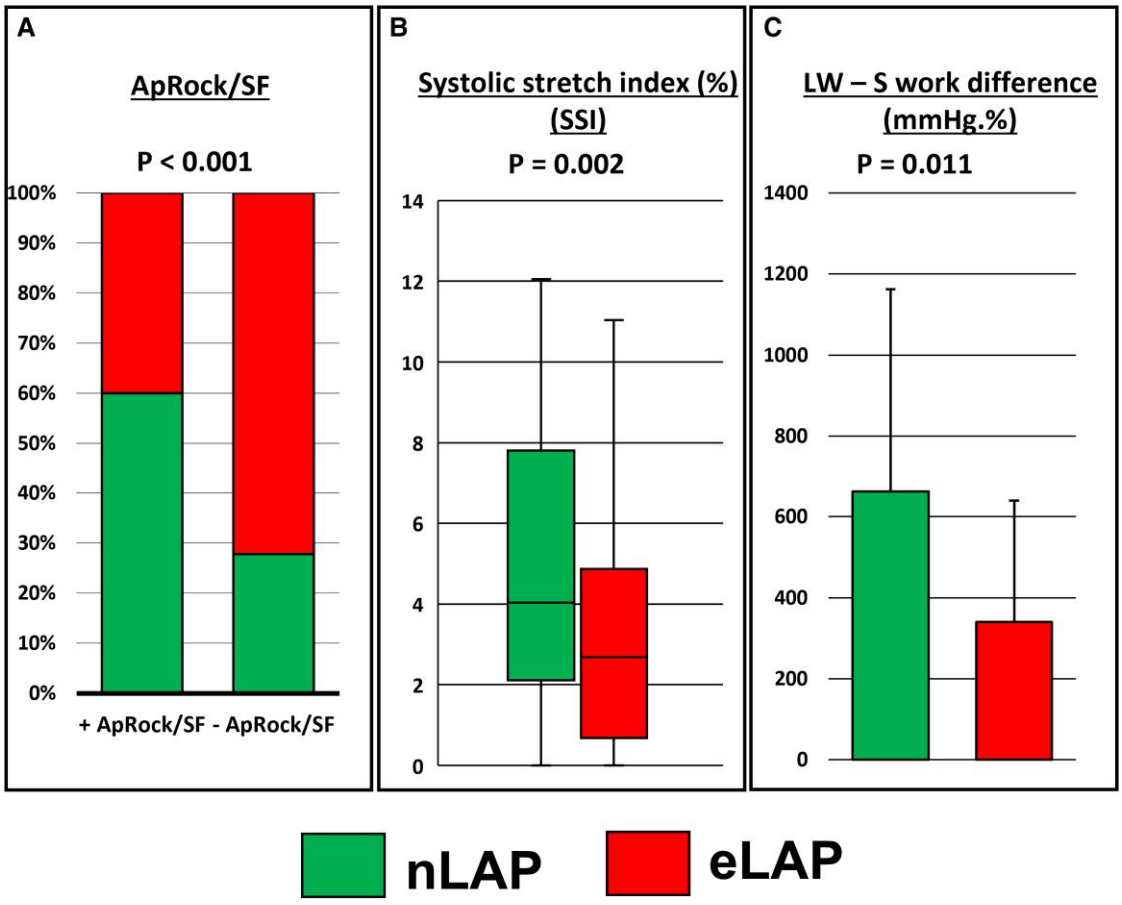


Figure 3 The association of estimated LAP, stratified into nLAP and eLAP , with ApRock/SF (*A*); SSI (*B*), and LW—septum (S) work difference (*C*).

Figure 3C. Similarly, there was significant association between nLAP and septal strain patterns 1 or 2 ($P = 0.01$). However, values of GWW did not differ between patients with nLAP and eLAP ($P = 0.09$) (Supplementary data online, *Figure S5*).

Predictors of CRT outcome

In multi-variable regression analyses for identifying predictor of LV reverse remodelling after CRT, ApRock/SF, and nLAP before CRT were the only independent predictors of the decrease in LVESV at CRT follow-up ($P = 0.043$ and 0.001, respectively, Supplementary data online, *Table S2*). On the other hand, independent predictors of lower all-cause mortality after CRT were ApRock/SF (hazard ratio: 0.42, confidence interval: 0.18–0.96, $P = 0.041$), AF ($P = 0.01$), and age at CRT implantation ($P = 0.003$, Supplementary data online, *Table S3*).

The prognostic value of the combined assessment of mechanical dyssynchrony and LAP on CRT outcome

In the present data, patients were further categorized into four groups based on the four possible combinations of the presence (+) or absence (−) of ApRock/SF, and the LAP category (nLAP or eLAP).

Patients with both nLAP and ApRock/SF showed significantly more pronounced reverse LV remodelling after CRT compared with patients with nLAP but no ApRock/SF ($P = 0.025$) and patients with eLAP and no ApRock/SF ($P < 0.001$, *Figure 4A*).

During follow-up, patients with both nLAP and ApRock/SF showed higher survival rates compared with patients with eLAP and ApRock/SF ($P = 0.037$) as well as patients with eLAP without ApRock/SF ($P < 0.001$), *Figure 4B*).

Virtual patient data

Impact of LV dilatation on filling pressure and mechanical dyssynchrony

Transitioning from the reference LBBB patient simulation (LVEF = 47%, mLAP = 5 mmHg) to LV dilatation with preserved contractility (LVEF = 33%) did not change filling pressure (mLAP = 5 mmHg). Mechanical dyssynchrony became more pronounced, as evident by increased values of SSI and LW-S work difference (*Figure 5*).

In contrast, the transition to the one with reduced contractility (LVEF = 33%) resulted in an increase of filling pressure (mLAP = 11 mmHg) as well as a decrease in the degree of mechanical dyssynchrony, characterized by decreased values of SSI and LW-S work difference (*Figure 6*).

Impact of intrinsic myocardial stiffness on filling pressure and mechanical dyssynchrony

Simulations also revealed that an increase of the intrinsic myocardial stiffness resulted in higher filling pressure and reduced mechanical dyssynchrony, irrespective of the type of LV dilatation (see *Figures 5* and *6*).

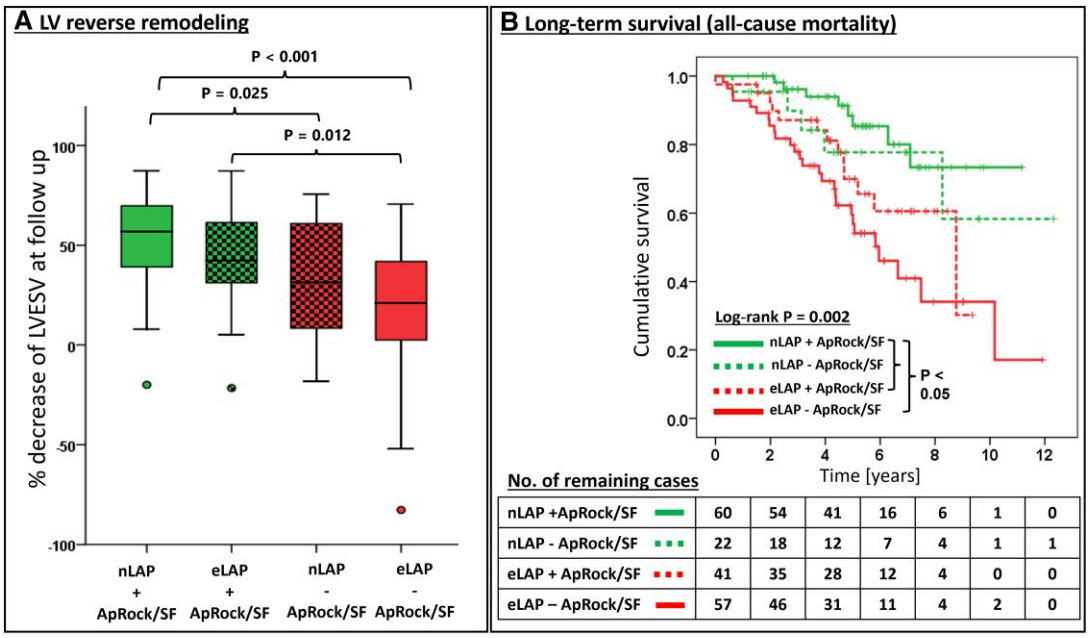


Figure 4 The association of the combined ECG-based assessment of ApRock/SF and baseline LAP (LAP) with CRT outcome in terms of CRT-induced reverse LV remodelling (*A*) and long-term survival (*B*). eLAP, elevated LAP; LVESV, left ventricular end-systolic volume; nLAP, normal LAP.

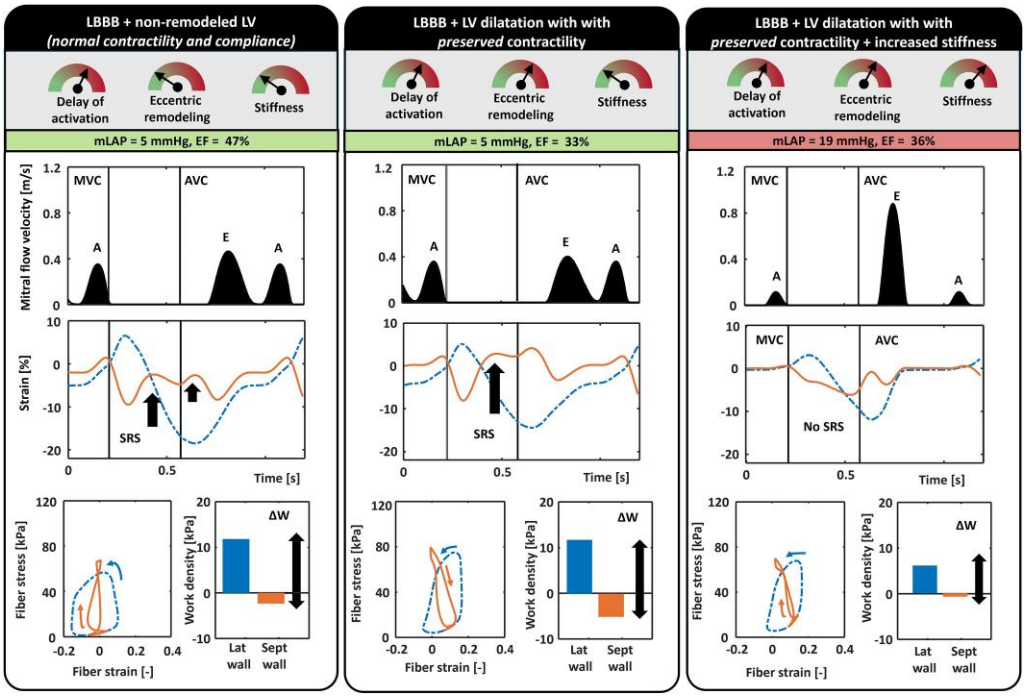


Figure 5 CircAdapt simulations showing the association between mLAP and mechanical dyssynchrony in three conditions; LBBB in non-remodelled heart (left panel), LBBB + LV dilatation with 'preserved' contractility (middle panel), and LBBB + LV dilatation with 'preserved' contractility + increased myocardial stiffness (right panel). Mitral inflow E and A waves are shown in the upper row. Mechanical dyssynchrony is expressed using LV longitudinal strain patterns of the septum and LW (middle row) and difference in work density between the septum and LW (lower row). AVC, aortic valve closure; MVC, mitral valve closure; SRS, systolic rebound stretch (represented by black arrows); ΔW, the difference in work between the septum and LW (represented by the double head black arrow).

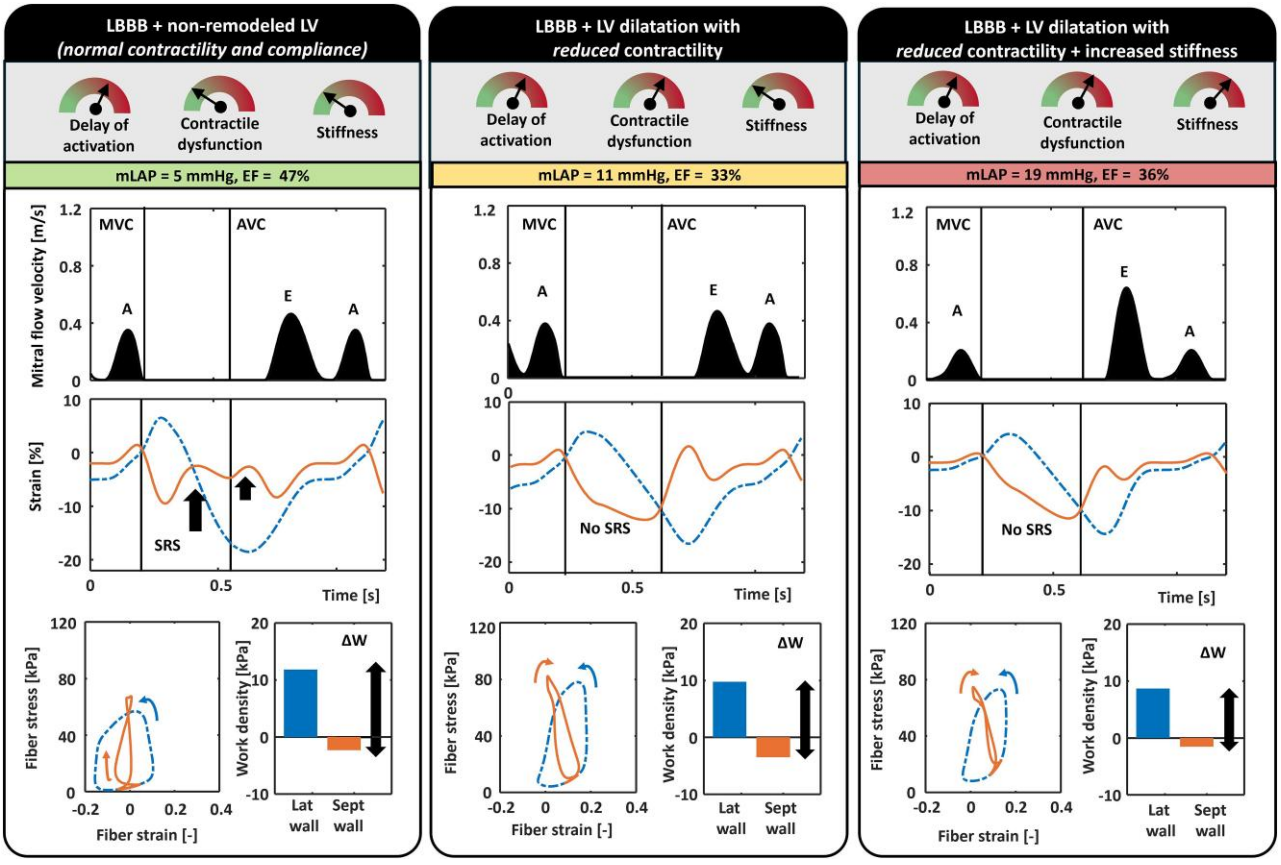


Figure 6 CircAdapt simulations showing the association between mLAP and mechanical dyssynchrony in three conditions; LBBB in non-remodelled heart (left panel), LBBB + LV dilatation with 'reduced' contractility (middle panel), and LBBB + LV dilatation with 'reduced' contractility + increased myocardial stiffness (right panel). Mitral inflow E and A waves are shown in the upper row. Mechanical dyssynchrony is expressed using LV longitudinal strain patterns of the septum and LW (middle row) and difference in work density between the septum and LW (lower row). AVC, aortic valve closure; MVC, mitral valve closure; SRS, systolic rebound stretch (represented by black arrows); ΔW, the difference in work between the septum and LW (represented by the double head black arrow).

Computer simulations additionally revealed an inverse linear relationship between SSI and Eed where virtual simulations with low SSI values were characterized by larger Eed (*Figure 7*).

Discussion

The association between LAP and mechanical dyssynchrony, a hidden interaction unveiled

In our study, we identified an association between mechanical dyssynchrony and normal filling pressure in CRT candidates. At first glance, this may seem counterintuitive, as mechanical dyssynchrony is generally linked to adverse cardiac conditions. However, our observation aligns with previous research, which has shown that the presence of mechanical dyssynchrony before CRT often correlates with more favourable outcomes post-CRT. This suggests that mechanical dyssynchrony serves as a marker of an electromechanical substrate that is responsive to CRT.[2,3,5,6,22] We extend this understanding by offering new mechanistic insights. Our study demonstrates that this electromechanical substrate reflects a structural and functional state of the ventricular tissue that is sufficiently contractile and compliant to enable the dynamic mechanical interaction between the early activated septal wall and the late activated LW induced by LBBB. This is further supported by the clinical profiles of our cohort, where patients with mechanical dyssynchrony displayed lower presence of ICM and reduced serum creatinine levels which are associated with myocardial stiffening. Moreover, our computer simulations confirmed that increased myocardial stiffness diminishes mechanical dyssynchrony, providing a mechanistic explanation for the observed relationship (*Graphical abstract*).

The impact of LV dilatation on both filling pressure and mechanical dyssynchrony

Previous data showed the association of novel indices of mechanical dyssynchrony including ApRock/SF, SSI, and regional myocardial work with CRT outcome.[4,5,22] Similarly, recent data showed the association between estimated LAP and CRT outcome.[7,8] However, the association between mechanical dyssynchrony and LAP has not been explicitly investigated.

Our simulations showed that in the setting of LBBB, the degree of mechanical dyssynchrony and mLAP were both dependent on the substrate of LV remodelling (characterized by LV dilatation with different levels of contractility and stiffness). Nevertheless, in contrast to simulations, a pure substrate of LV dilatation in CRT candidates is clinically

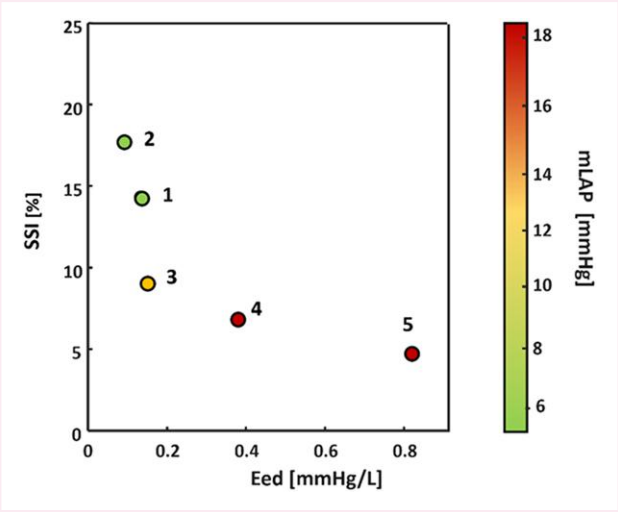


Figure 7 Scatterplot of the five virtual CRT simulations in our study, illustrating the negative correlation between SSI as an index of mechanical dyssynchrony and Eed as an index of operating chamber stiffness). The colour map represents the value of mLAP in each simulation. (1) LBBB in non-remodelled LV; (2) LBBB + LV dilatation with 'preserved' contractility; (3) LBBB + LV dilatation with 'reduced' contractility; (4) LBBB + LV dilatation with 'reduced' contractility + stiffness, and (5) LBBB + LV dilatation with 'preserved' contractility + stiffness.

barely identifiable yet, specific substrates may prevail over the process or remodelling (i.e. LBBB and ischaemic heart disease). In line with this hypothesis, recent data have proposed a strain-based identification of the predominant substrate of LV remodelling in CRT candidates with LBBB.[22] Their clinical data, supported by animal model experiments, suggests that highly pronounced patterns of mechanical dyssynchrony reflects a predominant LBBB substrate of LV remodelling. However, the relation with filling pressure was not investigated in their data.[22]

The broad scope of novel indices of mechanical dyssynchrony

Previous data showed that novel indices of mechanical dyssynchrony do not only reflect the electrical substrate of LBBB as well as the potential influence of different myocardial tissue properties like myocardial ischaemia and scar tissue on myocardial mechanics in LBBB,[2,23,24] they also reflect the pathophysiological continuum of LV remodelling in heart failure patients with LBBB.[22]

Our combined clinical-virtual patient data additionally suggests that clearly observed mechanical dyssynchrony in CRT candidates is an indication of LV remodelling with preserved myocardial compliance and lower operational stiffness and, hence, is amendable by CRT. This hypothesis is corroborated by our observation that the extent of reverse LV remodelling and the probability of survival are higher in patients with both mechanical dyssynchrony and nLAP than in patients with no mechanical dyssynchrony and eLAP at baseline. Our outcome data are in line with the data by Galli *et al.*[7] However, in their work, the association between mechanical dyssynchrony and LAP was not investigated.

Limitations

The main limitations of our study are the retrospective design and the relatively limited number of patients, yet with an extensive echocardiographic analysis of mechanical dyssynchrony, which was assessed both visually as well as fully quantified using strain-based and visual approaches. Additionally, invasive measurements of LAP were not available. Alternatively, we used the multi-parametric echocardiography-based guideline approach for grading LAP as nLAP or eLAP.[9] Based on the guideline document, this approach is generally discouraged in patients with LBBB or paced rhythm due to the absence of invasive validation.[9] However, the guideline algorithm was validated in a prospective multicentre study involving patients with various cardiac conditions. The echocardiographic approach demonstrated its ability to accurately identify patients with eLAP in patients with LBBB or a paced rhythm [area under the curve (AUC) = 0.84], with AF (AUC = 0.83), or with moderately severe to severe MR (AUC = 0.96).[10] This might support the use of this approach in our study, especially considering that invasive measurement of filling pressures is not routinely performed in clinical practice. Additionally, in a sub-group of patients, LAP could not be estimated (iLAP), which reflects an inherent limitation of the guideline algorithm. This issue has been noted repeatedly and often arises from technical challenges, such as poor Doppler signals or sub-optimal image quality, making some echocardiographic parameters difficult to measure.[9,10,25]

Conclusion

Our combined clinical-computational data demonstrated that mechanical dyssynchrony is reduced by contractile dysfunction as well as increased intrinsic stiffness of the LV myocardium, both increasing LV operational chamber stiffness and, hence filling pressure. In CRT candidates, evident mechanical dyssynchrony is therefore a marker of relatively preserved contractile and diastolic function, and is associated with better outcome. Conversely, the lack of mechanical dyssynchrony serves as an indicator of increased LV operational stiffness and elevated filling pressure, leading to an adverse patient outcome following CRT.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Conflict of interest: None declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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