Chronic heart failure patients with restrictive LV filling pattern have significantly less benefit from cardiac resynchronization therapy than patients with late LV filling pattern

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Abstract

\textit{Background:} Cardiac resynchronization fails to improve symptoms in up to one third of patients meeting criteria for this treatment, for reasons which are unclear. Indeed, the very mechanism of benefit from resynchronization is controversial. Resynchronization may work by improving ventricular filling; we tested the hypothesis that benefit from resynchronization depends on filling pattern.

\textit{Methods and results:} We assessed symptoms (NYHA class) and LV filling of 40 patients with chronic heart failure and prolonged QRS who underwent resynchronization. Fifteen had restrictive filling pattern (\(E\) velocity \(\geq 1.0\) m/s, \(E/A\) ratio \(< 1\) and \(E\) wave deceleration time \(\leq 140\) ms) and 25 had late filling pattern (single isolated \(A\) wave or summation wave filling in late diastole). At 6 months, the patients with restrictive filling failed to show the improvements observed in those with late filling. They failed to reduce NYHA class (\(\Delta\)NYHA: 27\% improved one class, 66\% unchanged, 7\% worsened one class, \(P=\text{NS}\)) vs. 8\% improved two classes, 72\% improved one class and 20\% unchanged, \(P<0.001\); difference between groups, \(P<0.001\)). They failed to reduce LV end-diastolic dimension (\(\Delta LVEDD = -0.04\) cm, \(P=\text{NS}\) vs. \(-0.6, P<0.001\); difference between groups, \(P<0.05\)) or end-systolic dimension (\(\Delta LVESD = -0.01\) cm, \(P=\text{NS}\) vs. \(-0.6, P<0.001\); difference between groups, \(P<0.05\)). They failed to improve cardiac cycle efficiency (\(\Delta\)total isovolumic [wasted] time 2.1 s/min, \(P=\text{NS}\); vs. \(-5.4\) s/min; difference between groups, \(P<0.001\)).

\textit{Conclusion:} Among patients routinely eligible for resynchronization, those with restrictive filling may show significantly less (and possibly no) improvement in symptom class and ventricular dimensions after resynchronization. Their failure to improve cardiac cycle efficiency may account for their attenuated clinical benefit.

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1. Introduction

A succession of trials has shown that groups of patients with heart failure and broad QRS duration have significant relief of symptoms from cardiac resynchronization therapy \[1\textsuperscript{-4}\] and subsequently show reduction in LV cavity size \[5\textsuperscript{-8}\]. Exactly which patients are most likely to benefit remains controversial. Large clinical trials may eventually address this question, but would be best designed in the light of a rational physiological basis for subgrouping patients. The inclusion criteria of the trials encompass a range of cardiac physiological states, and so permitting more than one interpretation of the mechanism of benefit from resynchronization.

The broad QRS, an entrance criterion for all of these trials, can delay the onset of mechanical contraction in
some segments of the ventricle, so that they are still shortening beyond the end of LV ejection. This delayed segmental shortening can impede ventricular filling in early diastole and can therefore leave ventricular filling heavily dependent on atrial contraction, which occurs late in diastole (“late filling pattern”) [9]. In some patients with heart failure and broad QRS, however, the elevation of left atrial pressures is severe enough to drive early diastolic filling (“restrictive filling pattern”). The exact response of these two physiologically different conditions to cardiac resynchronization therapy is not known, and may give insights into the mechanism of benefit of resynchronization. Whether patients with “late filling” and “restrictive filling” have similar or disparate responses to resynchronization depends on (and may be informative about) the mechanism of benefit of resynchronization.

One hypothesis of the mechanism of benefit from cardiac resynchronization is that it makes systole more efficient. Under this “global improvement” hypothesis, patients would be expected to benefit to a similar extent regardless of filling pattern. An alternative hypothesis is that resynchronization works primarily through enhancing time available for filling. This “improvement of filling time” hypothesis makes a specific testable prediction: benefit would depend on the type of filling pattern. In patients with broad QRS, the onset of systole in certain LV segments is delayed. Subsequently, systole continues beyond LV ejection into early diastole, thus blunting early ventricular filling [9]. In these patients, resynchronization therapy—by allowing filling to begin earlier—would have the best potential to enhance total filling. In contrast, if left atrial filling pressure is sufficiently elevated—enough to overwhelm segmental asynchrony—filling occurs early, is prompt and rapid (restrictive).

In this study we set out to examine whether there was a difference in response to resynchronization in symptoms, cardiac cycle efficiency, and in left ventricular dimensions between patients with restrictive filling and late filling.

2. Methods

2.1. Study design

In this prospective study, patients were identified through referral from heart failure clinics and enrolled over an 18-month period from August 2001 to February 2003. Patients were referred for resynchronization therapy based on symptomatic heart failure due to dilated cardiomyopathy and QRS prolongation on electrocardiography. All patients had clinical assessment, electrocardiography and echocardiography at baseline. Classification of LV filling pattern as restrictive or late diastolic was made at baseline.

Eligible patients were admitted for implantation of atrio-biventricular pacemakers. Prior to discharge, the programmed atrio-ventricular delay was optimized guided by Doppler echocardiography to maximize LV filling time. At 6 months, baseline observations were repeated. The patients and physicians who implanted the devices were blinded to classification of LV filling. The investigator reprogramming the device was also blinded to the filling pattern; although, the instructions given to them during echo-guided atrio-ventricular delay optimization were by a physician who could see the LV filling pattern on the echocardiograph monitor.

2.2. Patient eligibility

Patients were eligible if they had chronic heart failure due to either ischaemic or idiopathic dilated cardiomyopathy and had symptoms consistent with NYHA functional class III–IV dyspnoea. Patients who were classified as “unstable class II” patients (who often described class III symptoms) were also included. Patients had to be in sinus rhythm, have a left ventricular end-diastolic dimension of 5.5 cm or more, a left ventricular ejection fraction of 40% or less and a QRS duration of 130 ms or more. All patients had received the maximum tolerated medical therapy for heart failure which was stable for at least one month prior to pacemaker implantation. Medical therapy included angiotensin-converting enzyme inhibitors (or angiotensin II receptor blockers), beta-blockers and diuretics.

Patients were excluded if they already had a pacemaker or defibrillator prior to biventricular pacing, if they had a cardiac or cerebral ischaemic event 3 months prior to biventricular pacemaker implantation, or if they had a history of atrial tachyarrhythmia. The study was approved by the Royal Brompton and Harefield Hospitals ethics committee.

2.3. Echocardiographic evaluation and measurements

Resting transthoracic echocardiography was performed using a Philips (Andover, Massachusetts, USA) Sonos 5500 echocardiograph with a multifrequency transducer. Left ventricular transverse axis dimensions at end-diastole, LVEDD (onset of the q wave of the ECG), and at end-systole, LVESD (onset of the second heart sound on the phonocardiogram) were measured from the M-mode recording according to the recommendations of the American Society of Echocardiography. This was taken from the parasternal long axis view with the M-mode cursor positioned adjacent to the tips of the mitral valve leaflets, using leading edge methodology.

Doppler flow velocities were recorded from the apical four-chamber view, using the same transducer while in the pulsed wave Doppler mode, with the sample volume positioned at the tip of the mitral valve leaflets. Peak early and late diastolic flow velocities and total left ventricular filling time (time from the onset to the end of forward flow) were measured. LV filling was classified as restrictive according to a standard definition: E wave velocity greater than 1.0 m/s, E/A ratio greater than one and E wave
deceleration time less than 140 ms [10,11]. We pre-specified that the patients with a pseudonormal pattern would be classified as part of the restrictive group. When present, duration of mitral regurgitation was measured.

Left ventricular ejection time was measured from the LV outflow tract velocity profile. LV filling and ejection times were expressed as absolute values (ms) and as a product of their duration and heart rate, expressed in seconds per minute. The total isovolumic time (s/min) was calculated as: 60–(total ejection time+total filling time); these measurements are independent of heart rate [12]. The total isovolumic time represents the time wasted within the cardiac cycle when the LV is neither filling nor ejecting. All recordings were made at a speed of 100 mm/s with a superimposed electrocardiogram and phonocardiogram. Images were stored digitally and analyzed off-line.

2.4. Electrocardiography

All patients had standard 12-lead resting electrocardiogram, recorded on a Hewlett-Packard Xi Page Writer (calibration 0.1 mV/mm, paper speed 25 mm/s) on which QRS duration was measured using built-in computer software.

2.5. Device implantation

Patients were admitted 1 day prior to implantation of atrio-biventricular pacemakers (or atrio-biventricular pacemaker-defibrillators). Right ventricular leads were positioned at the RV apex. A venogram of the coronary sinus was performed to help optimize coronary sinus lead position. The target site was preferably the lateral wall of the LV, mid-way between its base and apex using the lateral vein. Other lateral and posterior sites were also accepted (postero-lateral or posterior vein). Lead positions were assessed and documented with a chest X-ray. Pacemakers were programmed to a therapeutic biventricular pacing mode (BV-DDD) and prior to discharge the programmed atrio-ventricular delay was optimized using Doppler echocardiography to maximize LV filling time, while ensuring atrial sensing and ventricular pacing, even at higher heart rates.

2.6. Statistical analysis

Primary endpoints of the study were NYHA functional class, LVEDD and LVESD. Secondary endpoints were total isovolumic time, LV filling time and LV ejection time.

Statistical calculations were performed using Statview 4.5 (Abacus Concepts, Berkeley, CA, USA). Continuous data are expressed as a mean±standard deviation. Statistical comparisons of continuous variables within groups and between groups were assessed using the paired and unpaired t-test, respectively. Comparisons of non-parametric variables were assessed using the Mann–Whitney U test for unpaired samples and the Wilcoxon Signed Rank test for paired samples. A P value of <0.05 was considered significant. Comparison of changes in variables between groups was performed by unpaired t-test. The predictive value of echocardiographic parameters and QRS duration for changes in the primary endpoints was determined using a simple linear regression model. When appropriate, a multivariate model was then constructed by a forward stepwise method.

3. Results

3.1. Patient population

Of 43 potentially eligible patients, 1 was excluded because resynchronization involved upgrading a pre-existing dual-chamber pacemaker and 2 were excluded because of they were in atrial fibrillation. Hence, 40 patients were enrolled in this study: 15 patients with restrictive filling (including 1 with pseudo-normalized LV filling) and 25 patients with late diastolic LV filling. The groups were comparable at baseline (Table 1) in age, sex, QRS duration, QRS morphology, LV dimensions, ejection fraction, NYHA class, aetiology of heart failure, blood pressure and medication profile. The range of systolic blood pressures of patients enrolled was between 80 and 154 mm Hg. As expected the patients with prompt early diastolic filling (restrictive filling pattern) had a shorter duration of functional mitral regurgitation. None of the 40 patients had significant (more than mild) mitral regurgitation. Among the patients with restrictive filling, E wave velocity was 1.2±0.2 m/s, E wave deceleration time was 113±19 ms and E/A ratio was 4.8±2.9.

3.2. Device implantation, coronary sinus lead position and pacing parameters

All 40 patients were successfully implanted with an atrio-biventricular pacemaker or a combined device (atrio-biventricular pacemaker-defibrillator). Adequate right atrial and right ventricular lead positions were achieved in all patients. Although two patients required coronary sinus lead repositioning due to loss of myocardial capture of pacing, acceptable coronary sinus lead positions were achieved in all forty patients. The type of pacing devices used, LV lead positions achieved and activation sequence proportions at follow-up did not differ between the two groups (see Table 1).

Two patients died before follow-up. Average follow-up time in the 38 remaining patients was 6.1±1.1 months. Over the follow-up period, mean atrial-sensed percentage was 76±30% and mean (bi-)ventricular-paced percentage was 98±3% in the group as a whole. There was no significant difference in these parameters between the two groups (see Table 1).
3.3. Effect of resynchronization in whole population

The effects of resynchronization on the whole population are shown in Table 2. NYHA class improved, with 62% of patients improving by at least one functional class ($P<0.0001$). Left ventricular cavity size fell, LVEDD by 0.34±1.6 cm ($P<0.01$) and LVESD by 0.41±0.9 cm ($P<0.01$). Ejection fraction increased by 8±16% ($P<0.001$). Efficiency of the cardiac cycle also improved, in that total isovolumic time shortened by 2.6±7.7 s/min ($P<0.01$) and LV filling time increased by 3.0±8.7 s/min ($P=0.01$). There was no
significant change in heart rate or LV ejection time after resynchronization.

On univariate analysis, none of the baseline echocardiographic parameters (LV filling time, ejection time, t-IVT, MR duration or ejection fraction) or QRS duration were significant predictors of improvement in NYHA functional class, LVESD or LVEDD.

3.4. Symptomatic response in restrictive and late filling patterns

The restrictive filling patients showed no significant improvement in NYHA class after resynchronization. In contrast, the patients with late diastolic LV filling had a significant reduction in NYHA class. These patients had a significantly greater reduction in NYHA class after resynchronization ($P<0.0001$, see Table 3).

3.5. Changes in ventricular dimensions in restrictive and late filling patients

While the restrictive filling patients showed no significant change in LV dimensions after resynchronization, the late filling patients did show significant reduction in both LVESD (from $6.1\pm1.3$ cm to $5.5\pm1.2$ cm, $P<0.001$) and LVEDD (from $7.3\pm1.1$ cm to $6.7\pm1.0$ cm, $P<0.001$) as shown in Fig. 1. There was a significant difference between restrictive filling and late filling patients in the change in ventricular dimensions after resynchronization, with $P<0.05$ for LVEDD and for LVESD on assessment by unpaired $t$-test (Table 3).

3.6. Changes in cardiac cycle timing in restrictive and late filling patients

Heart rate ($R-R$ interval) did not change in either group after resynchronization. In patients with restrictive filling, left ventricular filling and ejection times were unchanged. In patients with late filling LV filling, time increased from $334\pm149$ ms to $414\pm123$ ms, $P<0.001$ (or $23.3\pm5.6$ s/min to $28.9\pm5.9$ s/min, $P<0.0001$). LV ejection time did not change.

Total isovolumic time did not change after resynchronization in patients with restrictive filling but was significantly reduced in patients with late filling (from $18.0\pm4.7$ s/min to $12.6\pm5.7$ s/min, $P<0.0001$, Fig. 2). There was a significant difference between restrictive filling and late filling patients in the change in total isovolumic time and LV

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**Fig. 1.** Changes in LV end-systolic dimension (LVESD) and end-diastolic dimension (LVEDD), before and after resynchronization. Observations in individual patients with restrictive LV filling are shown on the top and those of the late diastolic LV filling group on the bottom. The heavy lines represent the changes in mean values and standard deviation of the mean. Comparisons before and after pacing were made by paired $t$-test.

**Fig. 2.** Changes in total isovolumic time. Observations of individual patients with restrictive LV filling are shown on top and those of the late diastolic LV filling group below. Mean changes and standard deviation of the mean are represented by the heavy lines. Comparisons before and after pacing were made by $t$-test.
filling time with resynchronization, with \( P=0.001 \) for total isovolumic time and \( P=0.002 \) for LV filling time (Table 3).

3.7. Reproducibility

The reproducibility of measurements used in our analysis has been published in a previous report by our department [5,12]. This study reported a coefficient of variation of 1–2% and 2–3% for intra- and inter-observer variability respectively for measuring LV ejection and filling times. The coefficients of variation were 10–11% (intraobserver) and 12–14% (interobserver) for measurement of LV cavity size.

4. Discussion

In this study we found that among patients with dilated cardiomyopathy and intraventricular conduction delay, those with restrictive pattern of left ventricular filling had a significantly smaller benefit from cardiac resynchronization, than patients with a late filling pattern. This smaller benefit manifested as no significant symptomatic improvement, no significant reverse remodelling and no significant benefit manifested as no significant symptomatic improvement in cardiac cycle efficiency (each significantly different from late filling patients).

These findings help narrow down the range of mechanisms of benefit from cardiac resynchronization therapy. Under the “global improvement” hypothesis, there would be no grounds for one filling pattern to respond differently from another. The limited peer reviewed data available in the literature include a post hoc analysis of fractional shortening in 19 patients, which found a greater increment in LV fractional shortening in patients with higher transmitral \( E \) wave velocity [13]. However, \( E \) wave velocity is neither monotonically related to severity of disease nor to left atrial pressure, and on its own is not an unambiguous classifier of physiological status. Moreover LV fractional shortening does not necessarily reflect symptomatic status and may be especially unreliable in the settings of asynchrony and of artificial resynchronization.

Our data favor the “enhancement of filling time” hypothesis over the “global improvement” hypothesis, since there appears to be a specificity of benefit to the late filling group rather than restrictive filling group (\( \Delta NYHA \) class \(-0.9 vs. -0.2, \Delta LVEDS \) \(-6 vs. 0 mm, \Delta LVESD \) \(-6 vs. 0 mm \)). These data are supported by another study which described significantly greater \( E \) wave velocities in non-responders (those who did not show LV reverse remodeling) to resynchronization [14].

Aside from these data, there are theoretical physiological grounds favoring the “enhancement of filling time” hypothesis. Left bundle branch block, regardless of ventricular cavity size, prolongs the isovolumic contraction and relaxation times at the expense of filling and ejection times \([15,16]\), thus grossly reducing the temporal efficiency of ventricular function. LBBB regionally delays onset of LV shortening so that parts of the ventricle are continuing to contract beyond the end of ejection, thus impeding LV filling during early diastole \([9]\). In some cases early diastolic filling can be completely suppressed (classic “late filling pattern”), leaving all filling to occur in late diastole (simultaneously with the atrioventricular contribution to filling) and thereby raising left atrial pressure and rendering the patient susceptible to breathlessness \([9]\). Cardiac resynchronization therapy brings about more uniform activation of the LV and therefore a more regionally consistent onset of relaxation. This has two benefits. First, more of the time and energy of LV shortening is applied productively in stroke volume ejection, rather than being wasted in early diastole.

Second, the alleviation of intra-ventricular tension during early diastole now allows the ventricle to fill more promptly rather than late in diastole (see Fig. 3). These effects prolong LV ejection and filling times and reduce the total isovolumic time, thus making the cardiac cycle more efficient. Therefore, under the “enhancement of filling time” hypothesis, patients with late filling would be expected to have a good chance of benefit.

The “enhancement of filling time” hypothesis also explains why the restrictive patients may have a smaller benefit. In restrictive filling, elevated left atrial pressure forces early diastolic filling to begin promptly after end of LV ejection. The elevated end-diastolic ventricular pressures then forces early cessation of passive filling (manifest as a short \( E \) wave deceleration time). The result of the short duration of this filling waveform is that even if additional time were available to it in early diastole, the net flow into the ventricle would not be increased.

The underlying processes involved in late filling and restrictive filling can co-exist. This means that some patients with restrictive filling and underlying intraventricular conduction delay could still benefit from resynchronization if, for example, addition of vasodilators were able to unmask latent late diastolic filling \([17]\). Hence, the pattern of ventricular filling represents the dominant physiological mechanism of impaired function; late filling suggesting delayed relaxation and restrictive filling suggesting raised atrio-ventricular filling pressures.

Failure of reverse re-modeling in the ventricles of patients with restrictive filling may result from failure to improve cycle efficiency (i.e. failure to shorten total isovolumic time). This possibility is supported by MUSTIC trial \([5]\) data which showed the temporal sequence of physiological events after resynchronization. First, total isovolumic time fell within 3 months (and fell no further thereafter). Then, LV cavity size fell and continued to fall for up to 12 months after resynchronization. In resynchronization, it may be the reduction of total isovolumic time and consequent increase in time available for filling which allows reverse re-modelling to occur.

How can these findings be reconciled with the multiplicity of trials showing clinical benefit from resynchronization? We believe it is noteworthy that there was a statistically
significant benefit in our patient population as a whole. This would accord with the benefit seen in previous larger trials. However, none of the large multicenter trials set out to systematically pre-classify patients according to filling pattern. Therefore our data are consistent with the possibility that within these trials, there existed a (large) minority of patients who may never have had much prospect for benefit.

4.1. Limitations

It may be a limitation of the study that it included a population with a mixed aetiology of cardiomyopathy. However, the proportions of ischaemic and non-ischaemic patients were comparable in the two groups. Similarly, other confounding factors which could potentially explain results, for example, ejection fraction, LV lead-tip position, blood pressure, medication profile and amount of therapeutic pacing during follow-up were comparable in both groups.

Patients were selected and grouped according to two distinct and dichotomous LV filling patterns. It is possible that some patients, who could be classified between these two paradigm groups, may demonstrate co-dominance of the mechanisms which limit ventricular function and therefore may demonstrate an intermediate functional response to resynchronization therapy.

Data was only available for a medium-term follow-up (6 months). Previous studies have demonstrated symptomatic improvement [3,7], reduction in total isovolumic time [12] and LV reverse remodeling [5,8] occur as early as three months and continue to improve up to one year after resynchronization. We therefore believe the findings at 6 months are a fair window over which to judge the medium-term effects of resynchronization.

4.2. Conclusions

Patients with restrictive left ventricular filling are unlike patients with late diastolic filling, in that they fail to show symptomatic benefit from resynchronization, fail to show reverse re-modelling of the LV cavity. We believe that this failure to respond is physiologically explicable on the basis of their lower potential to increase the quantity of filling when more time is made available for filling.

Fundamentally, the difference between the two groups may well be the relative importance of the two competing factors disrupting normal diastolic performance. When the dominant factor is pure dyssynchrony (which is potentially correctable with resynchronization) filling occurs late in diastole. When the dominant factors are elevated left atrial and end-diastolic pressures, filling occurs in early diastole with a restrictive pattern.

If large-scale trials substantiate this relationship between filling pattern and clinical benefit, then there will be several clinical implications. First, it may help provide physiological refinement to the criteria currently available for selecting patients for resynchronization. This may reduce the flow of patients (meeting the current indications) to resynchronization. Second, the size of the expected benefit in patients sub-selected using the additional filling pattern criteria would presumably be correspondingly greater, since it would be enriched for likely responders. Third, it may broaden the range of patients considered eligible for resynchronization to...
include patients with late filling from a variety of causes (not limited to broad QRS).

References