Sequential biventricular resynchronization optimized by myocardial strain rate analysis: a case report

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We report the case of a patient with severe left ventricular systolic dysfunction and left bundle branch block in whom cardiac resynchronization therapy (CRT) was optimized by tissue Doppler imaging. A horizontal mechanical asynchrony index was derived from tissue Doppler regional longitudinal strain rate profiles as the time difference at the onset of shortening between septum, lateral, anterior and inferior walls. The interventricular delay was modulated in order to achieve the smallest asynchrony index; on the basis of this parameter a sequential (S)-CRT with a left ventricular preexcitation of 20 ms was definitively programmed. This optimized S-CRT was followed by an acute improvement in systolic cardiac performance and by a long-term (12 months) clinical benefit as well as by a documented decrease in LV chamber size due to a true reverse remodeling effect. Thus, in some patients S-CRT may be more effective than conventional CRT. Tissue Doppler-derived strain rate analysis can provide information on the degree of left intraventricular asynchrony allowing the modulation of a tailored interventricular delay.

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Introduction

Cardiac resynchronization therapy (CRT) has been established as a therapeutic option in a subset of patients with dilated cardiomyopathy characterized by severe left ventricular (LV) systolic dysfunction and ventricular conduction delay leading to an uncoordinated contraction[1,2]. Simultaneous biventricular pacing is generally used for CRT [conventional (C)-CRT] but recent advances in pacemaker technology have made it possible to pace the ventricles independently [sequential (S)-CRT], so that an individualized interventricular delay may be programmed. Although pathophysiologic considerations and recently published data[3] suggest that S-CRT may be more efficient than C-CRT, the best modality of pacing is still subject of debate. In this report we present the case of a patient with dilated cardiomyopathy treated with S-CRT in whom analysis of the myocardial strain rate was used to noninvasively identify the LV mechanical asynchrony and to modulate the interventricular delay in order to optimize cardiac resynchronization.

Case report

A 70-year-old male with idiopathic dilated cardiomyopathy and normal coronary angiography was referred to our Cardiology Unit for the implantation of a biventricular pacemaker. At the time of admission, the patient was in NYHA functional class IV refractory to standard medical treatment, including maximized therapy with enalapril, carvedilol and furosemide. The electrocardiogram showed sinus rhythm, a PR duration of 190 ms and left bundle branch block with a QRS duration of 180 ms (Fig. 1A).

Pacemaker implantation. The patient underwent a dual-chamber pacemaker implantation with a recently developed device (Guidant, Contak 2 CHFD, Guidant Inc., St. Paul, MN, USA) which allows programming of the interventricular delay. Three transvenous pacing leads were inserted as follows: one was positioned in the right atrial appendage, a second one at the right ventricular apex, and a third unipolar lead with an over-the-wire system (Easytrak 2 Guidant) was advanced, after coronary sinus angiography, into the posterolat-

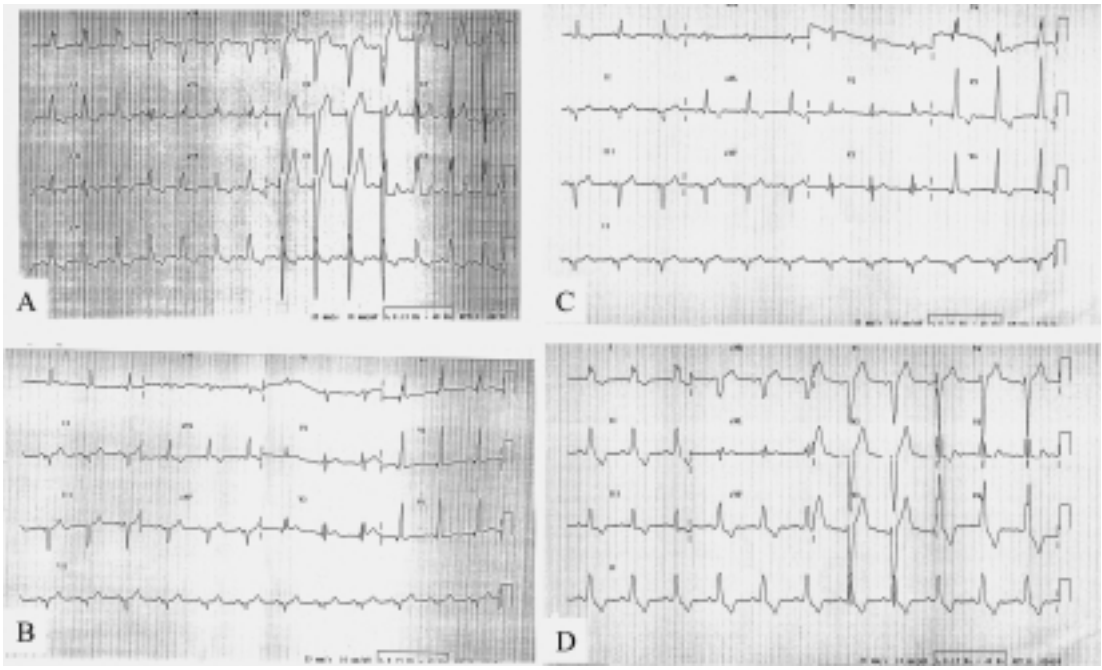

Figure 1. *Electrocardiogram before implantation* (A)*, at predisharge with an optimal sequential interventricular delay* (B) *and at 12 months of follow-up with biventricular pacing on* (C) *and off* (D)*. Note the marked reduction in the QRS duration from* A *(190 ms) to* B *and* C *(120 ms). When pacing was switched off, left bundle branch block with a wide QRS complex reappeared.*

eral cardiac vein. The pacing leads were connected to the dual-chamber biventricular pacemaker, which was programmed in DDDR mode.

Pacing optimization. At the first post-implant evaluation, the atrioventricular and the interventricular delay were optimized using the methods described by Ritter et al.[4] and Sogaard et al.[3], respectively. At each programmed interventricular delay (10, 20, 40 ms with the LV preexciting the RV and vice versa), an equilibrium period of 10 min was observed before ultrasound data acquisition. The definitive interventricular delay was selected using the ultrasound criteria described below.

Ultrasound image acquisition. The patient underwent a complete standard echocardiographic and conventional Doppler examination performed using a Vivid 5 echo scanner (GE-Vingmed, Horten, Norway) before pacemaker implantation. In addition, two color B-mode tissue Doppler cine-loops of the apical 4- and 2-chamber views, each including two consecutive cardiac cycles, were acquired at end-expiratory apnea and at a frame rate of about 150 frames/s. The cine-loops were then transferred to a computer for off-line analysis (EchoPac, GE-Vingmed, Horten, Norway). The ultrasound examination was repeated the day after pacemaker implantation and at 3, 6, and 12 months of follow-up.

Ultrasound image analysis. The regional longitudinal strain rate profiles were extracted from the recorded tissue velocity data set using a validated technique[5,6]. The cursor was positioned on the B-mode tissue Doppler images at the center of 4 basal LV segments, namely at the base of the inferior septum and of the lateral, anterior, and inferior walls. Then, two mechanical asynchrony indexes were calculated as the time difference between the onset of the systolic negative strain rate at the basal septum and lateral wall (S-L index) and at the basal anterior and inferior walls (A-I index)[7].

The following parameters were also calculated: LV end-diastolic and end-systolic diameters and volumes using the modified Simpson's rule; ejection fraction; total diastolic filling period; aortic time velocity integral (TVI); severity of mitral regurgitation (MR) using a 4-grade scale visual evaluation of the color Doppler regurgitant jet size in the 4-chamber view (MR score).

All measurements were performed before pacemaker implantation and repeated the day after and at 3, 6 and 12 months of follow-up (Table I).

In our laboratory, the intra- and interobserver variability of the strain rate indexes as above described is about 10%[8].

Pre-implantation, acute and follow-up data. Pre-CRT myocardial strain rate analysis documented the latest shortening deformation as occurring at the LV basal lateral wall (136 ms after the septum) (Table I, Fig. 2A). The optimal resynchronization was therefore defined as the smallest basal S-L index obtained by tailoring the interventricular interval, and was achieved by programming a LV pre-activation of 20 ms (Fig. 2C). At this programmed S-CRT, the longest LV total diastolic filling period and the highest aortic TVI and LV

Table I. Echocardiographic, Doppler and strain rate parameters measured at baseline (before implantation), at predischarge after simultaneous conventional and sequential biventricular pacing, and at 3, 6 and 12 months of follow-up.

	Baseline	C-CRT	S-CRT	3 months	6 months		12 months	
					BIV on	BIV off	BIV on	BIV off
LVEDD (cm)	7.5	6.4	6.0	6.0	5.6	5.8	5.5	5.7
LVESD (cm)	5.7	5.1	4.9	4.7	4.3	4.5	4.1	4.5
LVEDV (ml)	206	154	150	156	117	130	110	124
LVESV (ml)	155	107	92	98	65	75	58	70
LVEF (%)	25	30	38	38	45	42	47	43
LVTFP (ms)	290	320	360	418	363	327	468	345
AoTVI (cm)	16	20	22	26	25	20	26	22
MR score	3	2	2	2	2	2	2	2
HR (b/min)	80	80	72	72	73	75	63	66
S-L index (ms)	136	98	18	20	21	122	5	130
A-I index (ms)	38	22	32	5	5	30	15	28

A-I index = time difference in the onset of strain rate between the basal anterior septum and the inferior wall; AoTVI = aortic time velocity integral; C-CRT = conventional cardiac resynchronization therapy; HR = heart rate; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; LVTFP = left ventricular total diastolic filling period; MR = mitral regurgitation score: 1, mild; 2, mild-to-moderate; 3, moderate; and 4, severe regurgitation; S-CRT = sequential cardiac resynchronization therapy; S-L index = time difference in the onset of strain rate between the basal inferior septum and the lateral wall.

ejection fraction occurred the day after biventricular pacemaker implantation (Table I).

It should be noted that the asynchrony between the anterior and inferior walls (that is, the A-I index) was only minimally modified by acute biventricular pacing, whether simultaneously or sequentially induced; this could probably relate to the lesser extent of the pre-implantation A-I asynchrony compared to the S-L asynchrony. However, a more pronounced decrease in the A-I index was observed at long-term follow-up.

At 6 months of follow-up, a further decrease in LV dimensions and an increase in LV function (in terms of both aortic TVI and LV ejection fraction) were noted. The mechanical asynchrony indexes were similar to those achieved acutely after S-CRT. Interestingly, when pacing was temporarily switched off (30 min), the cardiac asynchrony indexes returned to the pre-CRT values, while the improvement in LV dimensions and systolic function persisted, indicating a true antiremodeling effect of S-CRT. This effect was also evident at 1 year of follow-up (Table I).

Discussion

Simultaneous C-CRT has recently emerged as a complementary treatment for patients with chronic heart failure and ventricular conduction delay, showing beneficial effects on the quality of life and several measures of LV systolic function[9,10]. A long-term positive impact on LV remodeling has also been documented after C-CRT[11]. Several issues, however, remain to be clarified, including the identification of the most appropriate CRT candidate and the modality of pacing (that is, simultaneous vs sequential)[3,12,13].

It has been assumed that CRT improves LV systolic function through a more synchronized ventricular contraction[14,15]. Therefore, the search for the appropriate CRT candidate should be based on techniques capable of detecting asynchrony in a delayed but still contracting LV myocardium. In this report we have used tissue Doppler imaging to acquire the myocardial velocities, which were then processed to obtain the regional longitudinal myocardial strain rate[5,6]. This parameter was applied to measure the spatial and temporal heterogeneity of LV contraction since it is much less affected by the overall and passive motions of the heart compared to myocardial velocities; strain rate, therefore, can actually allow differentiation between the delayed passive motion and active contraction of the LV myocardium at a regional level[16-18].

By using the strain rate mechanical asynchrony indexes in our patient, we have documented that before CRT the lateral wall shortening was substantially delayed compared to the septal shortening, and that this delay was only partially reduced by C-CRT from 136 to 98 ms (Fig. 2B). This large residual S-L asynchrony (98 ms) was further reduced by modulating the interventricular delay until the smallest value of the S-L index was reached, corresponding to a LV pre-activation time interval of 20 ms. Optimized S-CRT acutely produced the highest improvement in LV ejection fraction (38 vs 30% by C-CRT) and total diastolic filling period (360 vs 320 ms by C-CRT) (Table I); the clinical status of the patient also ameliorated, with the NYHA functional class decreasing from IV to II.

Compared to the short-term (3 months) follow-up evaluation, assessment at mid (6 months) and long-term (1 year) follow-up documented a further decrease in LV dimensions and an increase in ejection fraction

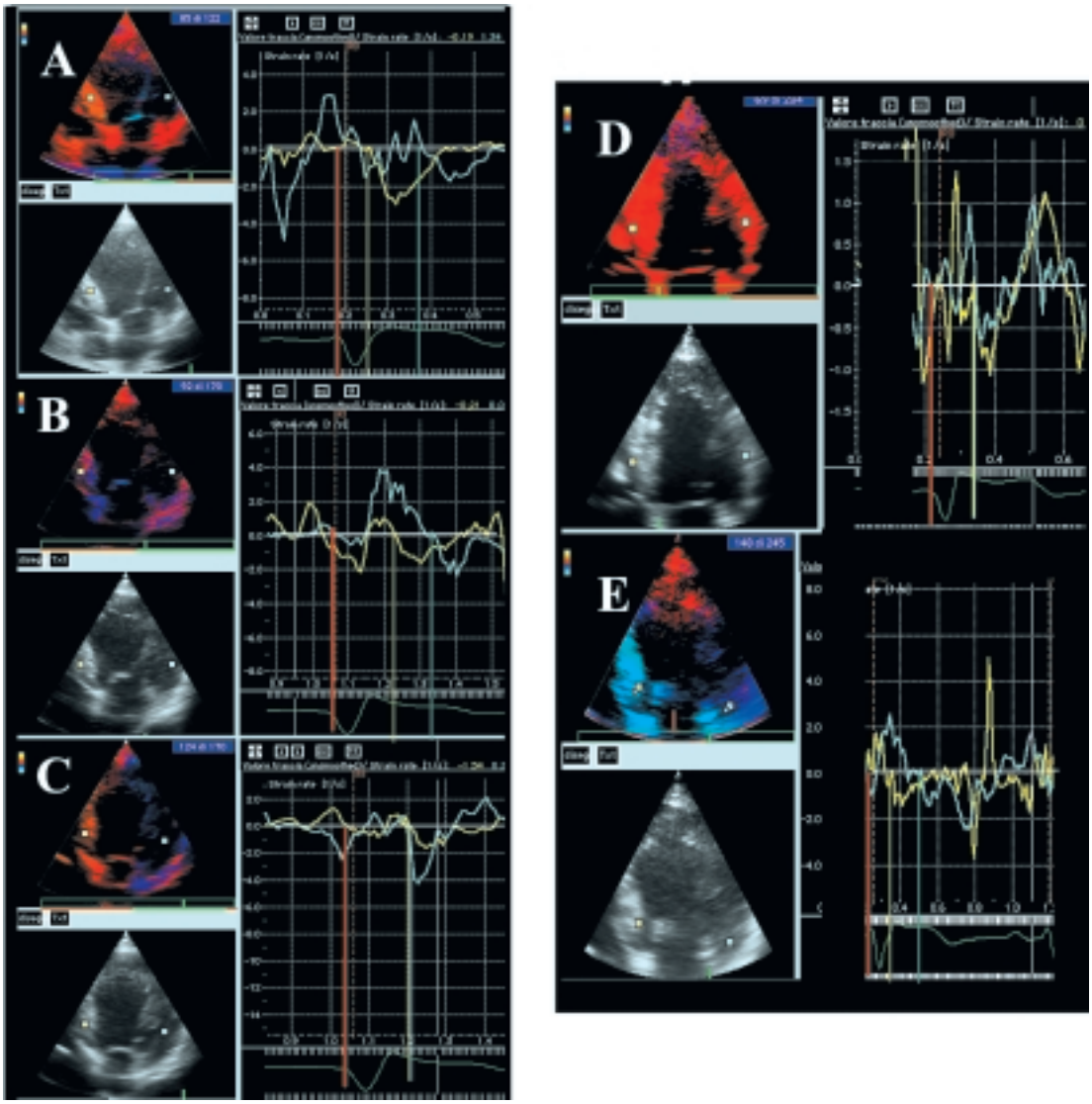

Figure 2. *Strain rate septal-lateral asynchrony measured as the time interval between the onset of the negative systolic strain rate at the basal septum* (yellow curve) *and the lateral wall* (green curve) *of the left ventricle. In each panel, the* vertical red line *identifies the QRS onset and the* vertical yellow *and* green lines*, the onset of the longitudinal systolic strain rate at the basal septum and lateral wall respectively.* A: *baseline strain rate curves.* B *and* C*: strain rate curves the day after biventricular pacemaker implantation with a non-optimized and optimized interventricular delay respectively.* D *and* E*: strain rate curves at 12 months of follow-up with the pacemaker switched on and off respectively. Note the reappearance of a severe horizontal septal-lateral asynchrony after interruption of pacing.*

(Table I). Interestingly, pacing interruption acutely worsened the S-L asynchrony while maintaining the improvement in LV volume and function (Table I). These results suggest, as pointed out by other authors[15], that the effects of optimized CRT may reflect a true reverse LV remodeling and not only a simple variation in the geometry of contraction. The mechanisms of reverse remodeling determined by CRT are still being debated; they may involve, at least in part, a reduction in the regional stress and stretch within the left ventricle due to the more coordinated and synchronous mechanical contraction, as well as a reduced sympathetic output, global end-systolic stress and MR[19]. Although we did not measure all these parameters in our patient, both the MR score and duration decreased immediately after therapy and during follow-up.

To the best of our knowledge, this is the first time that LV myocardial strain rate has been used to identify the optimal biventricular pacing modality for CRT. Therefore, we believe that specific aspects of this approach should be discussed in detail.

In our report, the beginning of the intrinsic regional myocardial deformation, as expressed by the longitudinal strain rate at its onset rather than at its peak, has been considered to define LV mechanical asynchrony. We are not aware of any studies that specifically compared the time-to-onset vs time-to-peak myocardial strain rate in the setting of dilated cardiomyopathies. In principle, one could expect the time-to-onset strain rates to be more related to the actual electromechanical delays but this, obviously, needs to be proved.

In addition to strain rate, myocardial strain may be used for the evaluation of LV mechanical asynchrony[18,20]. However, to avoid redundancy, we selected only one of these two parameters, namely the strain rate, basically because we were more confident with its use. Other authors[18] used strain in patients undergoing CRT to document the reversal of abnormal myocardial distribution of longitudinal deformation. It should be stressed that these two parameters are complementary for the evaluation of regional function when peak values are used (in fact, the peak strain represents the maximal myocardial shortening, normally occurring at end-systole, while the peak strain rate represents the maximal rate of myocardial deformation, generally occurring much earlier in systole). However, when onset values are used, the strain and strain rate could both be referred to the beginning of myocardial deformation.

Certainly, one of the most striking aspects of our case is the marked improvement in LV size and systolic function observed during patient follow-up. Apparently, the magnitude of this improvement is not in line with previous experiences from the literature[11,21] but it should be considered that, while data from the literature refer to averaged values from patient populations, we presented only an individual case that, most probably, lies at one side of the normal distribution of responders.

Finally, no changes in medical therapy were necessary during follow-up. Therefore, the observed long-term changes in LV dimensions and systolic function most probably represent a true effect of CRT.

Limitations. Similar to previous reports[22,23], our inter-observer variability appears to be relatively high; this represents, so far, the major limitation to the routine use of strain rate for the detection of left intraventricular asynchrony, despite the strong rationale for its clinical employment. It should however be noted that a recently introduced more sophisticated software, which does not rely on Doppler for strain rate calculation, may improve the reproducibility of this parameter, leading to a more widespread use of strain rate in the clinical setting.

In conclusion, our case suggests that in some patients with dilated heart failure and left bundle branch block, sequential CRT may be preferable to simultaneous conventional biventricular pacing. Strain rate analysis of asynchrony may be helpful to guide ventricular resynchronization, by both localizing and quantifying dyssynchrony and also by allowing a tailored interventricular delay.

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