Mechanical discoordination rather than dyssynchrony predicts reverse remodeling upon cardiac resynchronization

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Mechanical discoordination rather than dyssynchrony predicts reverse remodeling upon cardiac resynchronization therapy. Am J Physiol Heart Circ Physiol 295: H640–H646, 2008. First published May 30, 2008; doi:10.1152/ajpheart.00106.2008.—By current guidelines a considerable part of the patients selected for cardiac resynchronization therapy (CRT) do not respond to the therapy. We hypothesized that mechanical discoordination [opposite strain within the left ventricular (LV) wall] predicts reversal of LV remodeling upon CRT better than mechanical dyssynchrony. MRI tagging images were acquired in CRT candidates (n = 19) and in healthy control subjects (n = 9). Circumferential strain (εc) was determined in 160 regions. From εc signals we derived 1) an index of mechanical discoordination [internal stretch fraction (ISF), defined as the ratio of stretch to shortening during ejection] and 2) indexes of mechanical dyssynchrony: the 10–90% width of time to onset of shortening, time to peak shortening, and end-systolic strain. LV end-diastolic volume (LVEDV), end-systolic volume (LVESV), and ejection fraction (LVEF) were determined before and after 3 mo of CRT. Responders were defined as those patients in whom LVESV decreased by >15%. In responders (n = 10), CRT increased LVEF and decreased LVEDV and LVESV (11 ± 6%, 21 ± 16%, and 30 ± 16%, respectively) significantly more (P < 0.05) than in nonresponders (1 ± 6%, 3 ± 4%, and 5 ± 10%, respectively). Among mechanical indexes, only ISF was different between responders and nonresponders (0.53 ± 0.25 vs. 0.31 ± 0.16; P < 0.05). In patients with ISF >0.4 (n = 10), LVESV decreased by 31 ± 18% vs. 5 ± 11% in patients with ISF <0.4 (P < 0.05). We conclude that mechanical discoordination, as estimated from ISF, is a better predictor of reverse remodeling after CRT than differences in time to onset and time to peak shortening. Therefore, discoordination rather than dyssynchrony appears to reflect the reserve contractile capacity that can be recruited by CRT.

resynchronization therapy; cardiac mechanics

IN LARGE CLINICAL TRIALS cardiac resynchronization therapy (CRT) has been shown to improve cardiac function, clinical status, and survival significantly compared with placebo control subjects. However, of all patients receiving CRT ~30% do not respond clinically to this therapy (15–17) and an even larger percentage of patients do not show reverse remodeling (reversal of LV dilatation) (19, 27, 28).

Some studies suggested that mechanical dyssynchrony can improve prediction of response to CRT on top of wide QRS complex (15). However, an increasing number of studies, including the recent PROSPECT multicenter trial, seem to disprove this idea (5). We hypothesized that the imperfect prediction of CRT from mechanical dyssynchrony is due to the fact that pump function is dependent on coordination of contraction rather than on regional differences in timing of onset or peak of contraction.

To investigate this hypothesis we developed a novel measure of discoordination, internal stretch fraction (ISF), defined as the amount of stretch relative to the amount of shortening during ventricular ejection. ISF and conventional dyssynchrony measures were determined with MRI-myocardial tagging in a group of CRT patients, and the baseline values of the discoordination and dyssynchrony indexes were related to the long-term outcome (reverse remodeling) of CRT in these patients.

METHODS

Protocol: Patients and Control Subjects

A group of 19 patients (age 67 ± 8, male/female = 12/7), with [ischemic cardiomyopathy (ICM), n = 9] and without [dilated cardiomyopathy (DCM), n = 10] a history of ischemic disease and 9 healthy volunteers (control subjects) underwent measurements with tagged MRI. In patients, tagged MRI and echocardiography measurements (Philips Medical Systems) were performed 1 wk before the start of CRT and echocardiography was repeated 3 mo after the start to determine a change in LV end-diastolic volume (∆LVEDV), end-systolic volume (∆LVESV), and ejection fraction (∆LVEF) in the apical four- and two-chamber views. The degree of mitral regurgitation (MR) was assessed by color jet area and as mid-systolic percent jet area relative to left atrial size in the apical four-chamber view. The biventricular pacing leads (InSync 8042, Medtronic) at coronary sinus, right ventricle, and right atrium were positioned in a posterior or posterolateral branch, in the apical or midseptal region, and in the atrial appendage, respectively. The AV and VV delays were optimized as described previously (10, 11). Maximum rate of rise of LV pressure (dP/dtmax) was measured with a micromanometer introduced into the LV (RADI Medical Systems) (11). The ethics committee of the Catharina Hospital approved the study protocol, and all subjects gave informed consent.

MRI Scans

MRI images were acquired (Philips Medical Systems, 1.5 T) with a 500-ms acquisition period started 20 ms after the ECG trigger. In five parallel short-axis cross sections MR tagging image series (∆t = 20 ms) were acquired. The MR imaging parameters for each slice were as follows: echo time 10 ms, slice thickness 8 mm, field of view 213 mm, image size 256 × 256 pixels, and spatial modulation of the magnetization (SPAMM). Line tags were applied with intertag distance 5 mm, tag width 2.5 mm, and number of phases 16.

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Strain Measurements

Tagged MR images were processed off-line to obtain midwall circumferential strain ($\varepsilon_{cc}$) in 32 sectors in each slice with custom software written in Matlab 7.0 (7, 23). In the LV midwall the fibers are directed predominantly in the circumferential direction.

Each strain signal $\varepsilon_{cc}(t)$ was filtered with a low-pass filter with a cutoff frequency of 12.5 $s^{-1}$.

Data Analysis

Index of mechanical discoordination: internal stretch fraction. ISF was determined as the amount of stretch relative to the amount of shortening during the ejection phase. The “amount of stretch” was calculated as the product of the number of regions with stretch and their average amount of stretch, integrated over the ejection phase. A similar definition was used for the “amount of shortening.” The values of these variables are depicted as the size of the black and white areas under the curves in Figs. 1C, 2C, and 3C.

To calculate ISF, first from each strain signal $\varepsilon_{cc}(t)$ (Figs. 1A, 2A, 3A) a strain rate signal $e(t)$ was derived by time differentiation (Figs. 1B, 2B, 3B). Then the strain rate signals were split into a lengthening signal $e_p(t)$ and a shortening signal $e_n(t)$ with

$$e(t) = \frac{de_{cc}(t)}{dt} \quad e_p(t) = \max(0,e(t)) \quad e_n(t) = \min(0,e(t))$$  \hspace{1cm} (1)

Averaging $e_p(t)$ and $e_n(t)$ over all 160 signals resulted in average lengthening $\varepsilon_p$ and average shortening $\varepsilon_n$, respectively (Figs. 1B, 2B, 3B). Integration of these signals in the time interval $[T_1, T_2]$ (Fig. 1C) results in a strain $\varepsilon_p$, representing the amount of stretch, and a strain $\varepsilon_n$, representing the amount of shortening:

$$\varepsilon_p = \int_{T_1}^{T_2} e_p(t)dt \quad \varepsilon_n = \int_{T_1}^{T_2} e_n(t)dt$$  \hspace{1cm} (2)

We calculated ISF during the ejection phase; therefore, $T_1$ was the start (begin ejection, BE) and $T_2$ the end (end ejection, EE) of the ejection phase. BE and EE were determined from the pattern of the frame rate.

Indexes of mechanical dyssynchrony. From each strain signal three parameters were determined. 1) Onset of shortening time ($T_{onset}$) was determined by the first positive-to-negative zero crossing of strain rate $e(t)$ as defined in Eq. 1. 2) Time to the first peak of shortening ($T_{peak}$) was determined by the first negative-to-positive zero crossing of $e(t)$ after $T_{onset}$. 3) End-systolic strain ($\varepsilon_{ES}$) was determined as the value of $\varepsilon_{cc}(t)$ at $t = T_{ES}$. To increase the precision of determination of $T_{onset}$ and $T_{peak}$, the values of $\varepsilon_{cc}(t)$ time derivatives between two points were linearly interpolated. This approach yields $T_{onset}$ variability within $\pm 5$ ms (26).

Equations 1–3 were implemented numerically by discretization to the frame rate.

Fig. 1. Measured data and explanation of ISF concept for representative healthy control subject. A: tracings of circumferential strain ($\varepsilon_{cc}$) in all 160 regions. B: tracings of strain rate (thin gray lines) and the time course of the average lengthening $\varepsilon_p$ (solid black line) and average shortening $\varepsilon_n$ (dotted black line). C: the amount of stretch ($\varepsilon_p$) and shortening ($\varepsilon_n$) during ejection phase are represented with the area below the curve $\varepsilon_p$ (black area) and above the curve $\varepsilon_n$ (white area), respectively, BE, begin ejection; EE, end ejection.

Fig. 2. Measured data and explanation of ISF concept for representative responder patient. For figure explanation see Fig. 1.

AJP-Heart Circ Physiol • VOL 295 • AUGUST 2008 • www.ajpheart.org
Subsequently, $WT_{\text{onset}}$, $WT_{\text{peak}}$, and $W_{\varepsilon_{\text{ES}}}$ were determined as the width of the interval between the 10th and 90th percentiles of $T_{\text{onset}}$, $T_{\text{peak}}$, and $\varepsilon_{\text{ES}}$, respectively. The width of these intervals reflects the degree of the mechanical dyssynchrony (25).

$WT_{\text{onset}}$ and $WT_{\text{peak}}$ are measures of intraventricular mechanical dyssynchrony, which are the equivalents of those determined with tissue Doppler velocities (4, 15, 28, 29). $W_{\varepsilon_{\text{ES}}}$ was determined as well, because variation in $\varepsilon_{\text{ES}}$ is also increased within dysynchronous ventricles (24).

Statistics. Patients were divided post hoc into two groups, responders and nonresponders, defined as subjects with $\Delta LVEDV > 15\%$ and $\Delta LVESV \leq 15\%$, respectively. Subsequently, all data were pooled within control, responder, and nonresponder groups. All data are presented as means $\pm$ SD. Differences between groups were evaluated with one-way ANOVA; $P < 0.05$ was considered statistically significant. Changes over time within a group were analyzed by paired $t$-test.

RESULTS

Clinical Variables

All patients survived during follow-up. By the criterion of a decrease in LVESV $> 15\%$ (see Statistics), 10 of 19 patients were responders and 9 were nonresponders. Of the responders 8 of 10 had DCM, and of the nonresponders 7 of 9 had ICM. Absolute values of clinical and echocardiographic variables are summarized in Table 1. Baseline characteristics were similar between the responder and nonresponder groups. Both groups improved clinically, as indicated by the decrease in $\text{NYHA class}$. However, 3 mo of CRT only significantly increased 6-min walk test, cardiac index, and LVEF and significantly decreased LVESV in the responder group (Table 1).

Reverse Remodeling After 3 Months of CRT Is Associated with High ISF

Both patient groups had significantly elevated values of $WT_{\text{onset}}$, $WT_{\text{peak}}$, $W_{\varepsilon_{\text{ES}}}$, and ISF compared with the control group (Fig. 7). ISF values were significantly different between the responders and nonresponders. However, the two patient groups did not significantly differ with regard to any of the

Figure 5 presents the percent decrease in LVEDV and LVESV and the change in LVEF after 3 mo of CRT and the percent increase of $d\varphi_n/dt_{max}$ acutely upon CRT. Responders had significantly larger decrease in LVEDV and LVESV ($\%\Delta LVEDV$, $\%\Delta LVESV$, respectively) and a larger increase in LVEF, but the acute increase in $d\varphi_n/dt_{max}$ ($\%\Delta d\varphi_n/dt_{max}$) was similar in both groups.

Strain Analysis

Figures 1–3 show examples of strain analysis in three individuals. Within the LV wall of the healthy control subject $\varepsilon_{cc}(t)$ signals were similar (Fig. 1A). In contrast, within the LV wall of the two patients (Figs. 2A and 3A), the strain signals were unalike. The amount of stretch [$\varepsilon_p(t)$, solid line] and shortening [$\varepsilon_n(t)$] is shown in Figs. 1B, 2B, and 3B. In the control subject, during ejection $\varepsilon_p(t)$ was negligible and $\varepsilon_n(t)$ was large and the opposite was true during the filling phase. In contrast, in the patients $\varepsilon_p(t)$ was substantial, especially during early ejection in the responder patient.

Figure 6 shows examples of the regional distribution of ISF, $T_{\text{onset}}$, and $T_{\text{peak}}$. In the healthy control subject maps are almost uniform. In both the responder and nonresponder patients the yellow-red areas in the $T_{\text{onset}}$ and $T_{\text{peak}}$ maps indicate regions with delayed onset and peak shortening, respectively. In both patients, maps of $T_{\text{onset}}$ and $T_{\text{peak}}$ appear similar. In contrast, only in the responder patient is a region with high values of ISF observed, located predominantly in the anterior septum.
other mechanical indexes or QRS duration or LVESV at baseline.

Figure 8 presents the individual values of the indexes of reverse remodeling (%ΔLVEDV, %ΔLVESV, and ΔLVEF) as a function of ISF and WT_onset. In Fig. 8, top left, it is shown that all but two responders had an ISF >0.4 and all but two nonresponders had an ISF <0.4. When the patients were divided into groups with ISF >0.4 and ≤0.4, the resulting groups with a high ISF (0.62 ± 0.14, n = 10) had significantly more ventricular reverse remodeling than those with a low ISF (0.22 ± 0.10; P < 0.05): %ΔLVESV = 31 ± 18% vs. 5 ± 11%, %ΔLVEDV = 20 ± 16% vs. 3 ± 5%, and ΔLVEF = 10 ± 6% vs. 1 ± 6%, respectively (all P < 0.05). Figure 8 also shows that most ICM patients have lower ISF than most DCM patients, but there is some overlap between the data points of these two disease categories.

In contrast, the value of WT_onset was not associated with any of the reverse remodeling parameters, as shown in Fig. 8, right. When the patients were divided in groups with WT_onset greater than and less than or equal to the median of WT_onset (0.08 s) (WT_onset: 0.09 ± 0.01 s vs. 0.06 ± 0.01 s, respectively; P < 0.05), no difference between groups with high (n = 10) and low WT_onset was found: %ΔLVESV = 20 ± 21% vs. 17 ± 19%, %ΔLVEDV = 12 ± 16% vs. 12 ± 14%, and ΔLVEF = 8 ± 8% vs. 4 ± 8%, respectively.

**DISCUSSION**

The present study demonstrates that the baseline value of the discordiation index ISF provides a prediction of reversal of LV remodeling that is considerably better than that from conventional indexes of mechanical dyssynchrony or from the acute increase in contractility (dwp/dtmax). Therefore, these data support the idea that an index of discordiation can contribute importantly to a good prediction of the volume response to CRT. Moreover, the lack of such prediction by the indexes of mechanical dyssynchrony may at least partly explain the limited added value of indexes of echocardiographically determined mechanical dyssynchrony to predict response to CRT (5).

Reduction of dilatation indicates structural recovery at the organ level. Absence of an increase in LVEF or a decrease in LVESV does not exclude a beneficial effect of CRT on the clinical status of the patient. This can be derived from the significant decrease in NYHA class in the responders and nonresponders in our study. However, the NYHA class is
subject to a placebo effect (1), and the most pronounced improvements, including improved survival, prevail in patients with reduction of dilatation (27).

The mechanical discoordination may have two origins: asynchrony of activation as a result of conduction disorder and/or regional deterioration of contractility as a result of ischemia or infarction (12). Of the two only the former can be compensated by CRT. The infarcted myocardium forms scar, which is less compliant than viable nonactivated tissue and hence at raised pressure stretches less. The scar tissue cannot be recruited by CRT and does not contribute considerably to ISF value.

The ISF Concept

The observation that ISF is related to the increase in LVEF supports the idea that reduction of opposing systolic strain patterns leads to more effective ejection of blood into the arterial circulation. It is plausible that such a better ejection helps to let the LV operate at a smaller volume, thereby allowing a decrease of LV dilatation in the long run.

Figure 8 shows that CRT response can be predicted from the ISF value but, however, also fairly well from the disease categories DCM and ICM alone.

Preliminary results from animal experiments in our laboratory show that ISF increases because of creation of left bundle branch block (LBBB) but not because of chronic infarction. Therefore, a low ISF may indicate the absence of LBBB (even despite a wide QRS complex). An alternative explanation would be that in asynchronous ventricles large opposing strains are reduced because of increased myocardial stiffness. The source of this increased stiffness may be scar tissue resulting from infarctions. The amount of scar varies largely among ICM patients, some having no scar at all. Other sources of decreased myocardial compliance may be generalized fibrosis, as a result of myocardial remodeling, and altered properties of titin (14).

Such generalized changes have been reported for various abnormal cardiac overload conditions (hypertension, valvular disease, heart failure) and may therefore explain the low ISF in some of the DCM patients. Clearly, future studies are required to investigate the cause of low ISF values in asynchronous hearts in more detail.

A theoretical advantage of ISF over conventional measures of mechanical dyssynchrony is that it takes into account regional dispersion of strain throughout the entire ejection phase, rather than at a single time point in a strain signal. A practical advantage of this difference is also that when using ISF one does not rely on proper detection of the onset or peak of shortening, which can be problematic in cases of gradual changes, noisy signals, and low sampling rates.

In our study strain was determined in 160 regions within 5 short-axis slices of the LV wall, covering at least 70% of that wall. Nowadays, myocardial strains can also be determined with speckle tracking, and such strains can, theoretically, be used equally well for ISF analysis. The ISF maps in Fig. 6 show that the major dispersion of ISF occurs in the septum-to-lateral wall direction, so ISF could be reliably determined with a few well-chosen echocardiographic sections.

Besides discoordination in ventricular mechanics during ejection phase there is also discoordination during filling phase. In Figs. 2A and 3A, we can see both as opposite strain slopes during each phase. We determined the amount of discoordination during filling phase with ISFd, which is a conceptual equivalent to ISF. ISFd was calculated as a ratio between the amount of shortening and stretch (inversely to ISF). ISFd is not as predictive for the CRT outcome as ISF. Although there are differences between responders and nonres-
sponders in ISFd (0.54 ± 0.22 vs. 0.40 ± 0.16, respectively) they are not significant.

ISF is conceptually related to internal flow fraction (IFF), estimated from measurements of longitudinal segmental volume change by the conductance catheter technique. IFF was shown to be increased in heart failure patients with conduction disorders and reduced during CRT (20, 21), but a relation with long-term response to CRT has not been published until now. It is the advantage of ISF that it can be measured noninvasively and that septal-to-lateral wall differences are taken into account.

The TUS (or CURE) index also includes information about coordination (18). This index is calculated with Fourier analysis of strain in LV regions in space. The TUS index reflects the relative first-order Fourier power within the LV wall. In doing so, TUS assumes a sine wave spatial variation in strains and it does not express the amount of stretch. ISF is calculated without any assumption on distribution of strain in space and time.

Other studies have employed a vector analysis of mechanical dyssynchrony (9, 13, 25). This reflects the main orientation of the major component of dyssynchrony, but again does not reflect the amount of stretch.

**Mechanical Dyssynchrony**

A large number of single-center studies have reported that septal-to-lateral delay and/or the standard deviation of the time to peak velocity values of 12 segments have a high sensitivity/specificity to predict CRT responders (3). However, the recent PROSPECT multicenter study (5) and several smaller single-center studies show that the prediction of responders is moderate and hardly better than that by QRS width alone (2, 3, 6, 18). On the basis of these findings, a recent group of experts declared in a consensus statement on behalf of the American Society of Echocardiography that the decision for treating a patient with CRT should not be based on or withheld because of results of an echocardiographic Doppler dyssynchrony study (8).

An extensive discussion about the possible explanations of the current confusion in this area is beyond the scope of this article. Relevant to the results from the present study is that it has been argued that the poor performance of the indexes would, in part, be related to limitations of tissue Doppler imaging (TDI) and other echocardiographic techniques and potential subjective aspects in the analysis (6). In the present study we determined mechanical dyssynchrony with MRI tagging, the gold standard of myocardial deformation, and using completely objective analysis. The only manual, subjective, part in the entire analysis was the manual contouring of endocardial and epicardial borders of the LV wall in order to create the region of interest. Moreover, we used MRI tagging measurement covering a large part of the LV wall and with a high spatial resolution, making it unlikely that important information was missed. Despite the use of this state-of-the-art technique for measuring myocardial strains, the indexes related to a single point in time (time of onset or peak shortening, value of strain at end systole) did not differentiate between responders and nonresponders. This observation suggests that the disappointing results of various recent echocardiographic studies on prediction of CRT response may, in part, be explained by the use of timing parameters and that potentially the use of indexes of dyssynchronization may improve prediction of CRT response.

**Indexes of Mechanical Dyssynchrony**

We used WT measures based on 10th–90th percentile intervals, which is a rather sophisticated approach compared with more traditional parameters like septal-to-lateral delay. It can be seen in Fig. 6 that there is quite some variation in $T_{\text{peak}}$ and $T_{\text{onset}}$ along a hypothetical ultrasound beam in the basal septal and lateral wall. Accordingly, the value of the septum-to-lateral wall delay is heavily dependent on the regions chosen and is therefore less likely to predict CRT response. We considered it fair to the dyssynchrony measures to use a measure that takes into account the variation in all regions, similar to the case with ISF.

**Mitral Regurgitation and ISF**

In this study we determined ISF only during the ejection phase, hence avoiding isovolumic contraction and relaxation phases where most of the effect of MR happens. In case of MR during the ejection phase, this would reduce the value of ISF, since shortening does not discriminate between ejection into the aorta and atrium. In exploring the best possible criteria, we also investigated whether calculation of ISF during the entire systole, including the isovolumic phases, would improve prediction of CRT response, and this was not the case.

**Predictive Value of $dP/dt_{\text{max}}$**

In various scientific studies as well as in some clinical practice $dP/dt_{\text{max}}$ is being used to test the acute hemodynamic effect of CRT (11). While this information is most likely relevant, there is, to our knowledge, no publication showing the correlation between the acute hemodynamic effect and long-term reverse remodeling. In contrast, already in 2001 Stellbrink et al. (22) reported that acute hemodynamic improvement did not predict long-term reverse remodeling. Therefore, the finding in our small group of patients that the acute hemodynamic response does not predict long-term reverse remodeling is not necessarily in conflict with other data in the literature. It should, however, be kept in mind that this study was by no means designed to investigate this question. Obviously, larger studies are required to investigate this question in more detail.

**Critiques on the Study Design**

We chose to study the feasibility of the ISF analysis by using the best technique to measure myocardial strains, the relatively expensive and complex MRI tagging technique. As a consequence, the number of patients included in the study was relatively small. Therefore, only differences between the two patient groups can be compared, as opposed to determining specificity and sensitivity. Despite the small groups, ISF proved to be consistently different between responders and nonresponders, whereas conventional indexes of mechanical dyssynchrony did not differentiate at all between responders and nonresponders.

The data in Fig. 8 show that the presence of ICM was also predictive of nonresponse to CRT. To what extent ISF is...
coupled to ICM and DCM and whether ISF is a better predictor than ICM/DCM should be proven in a larger study, which is currently being performed.

The patients included in this study can be regarded as typical CRT patients because of their degree of heart failure (NYHA class III) and QRS width (~160 ms), and all showed a clear increase in $\Delta p_v/\Delta d_{\text{max}}$ immediately on the start of CRT. It remains to be explored whether ISF can also be useful in the selection of patients with more moderate degrees of heart failure.

Conclusions

All indexes of dysynchrony and discoordination ($W_{\text{onset}}$, $W_{\text{peak}}$, $W_{\text{ES}}$, and ISF) discriminate normal from asynergic hearts. However, the discoordination index ISF is the only one of these parameters that discriminates between patients in whom CRT does or does not reverse LV dilatation. Discoordination rather than dysynchrony appears to reflect the reserve contractile capacity that can be recruited by CRT.

REFERENCES


