This article discusses how echocardiography can be applied to quantify dyssynchrony in patients who are evaluated for cardiac resynchronization therapy (CRT). A number of echocardiographic indices have been proposed as markers of success of CRT. However, when tested against QRS width in prospective clinical trials, none of the echocardiographic indices are proven to give clinical benefit. One important message in this review is that future studies should focus on approaches which can differentiate between electrical and non-electrical aetiologies of dyssynchrony, since only electrical dyssynchrony is likely to respond to CRT. Just measuring velocity indices does not identify the aetiology. Myocardial strain appears more promising, but one should be aware that timing of peak systolic strain is determined not only by electrical conduction. It is proposed to use onset septal shortening during pre-ejection for timing of earliest left ventricular (LV) electrical activation. One should take into account potential ischaemia, scarring, and other structural changes as contributors to dyssynchrony. As a method to identify electrical dyssynchrony, the authors propose to use time of active force generation as defined by LV pressure-strain loops. A non-invasive method to measure segmental pressure-strain loops is also proposed as a means to quantify the impact of dyssynchrony on distribution of myocardial work. Furthermore, it is important to be aware that LV dyssynchrony may have a combination of aetiologies, not all amenable for CRT.

Keywords

Echocardiography • Dyssynchrony • Myocardial function • Cardiac resynchronization therapy

Introduction

In patients with heart failure and left ventricular (LV) intraventricular dyssynchrony, cardiac function can be improved by electrically activating the septum and the lateral free wall in a synchronized manner with a biventricular pacing device, a treatment named cardiac resynchronization therapy (CRT). In selected patients with congestive heart failure, CRT causes reversal of LV remodeling, improvement of symptoms, and reduction in mortality. Furthermore, CRT tends to reduce mitral regurgitation. However, about one-third of patients treated with CRT do not show clinical improvement, indicating that we need better methods for identifying those who will benefit from the therapy.

Identification of CRT responders can be done by two different principles, i.e. by assessing either electrocardiographic or cardiac mechanical signs of dyssynchrony. At the present time, electrocardiographic criteria are used as the main screening tools, and patients with congestive heart failure and ejection fraction <35% are selected for CRT based on morphology and duration of the QRS complex. In clinical trials that have documented clinical benefit of CRT, one of the entry criteria has been QRS duration over 120 ms, and average QRS duration in the large trials has been over 150 ms, most often with left bundle branch block (LBBB) type morphology and sinus rhythm. There is not sufficient documentation to recommend CRT in patients with pure right bundle branch block. Several trials have shown that QRS is not a very precise marker of LV dyssynchrony, as patients with a wide QRS may not have LV dyssynchrony and those with a narrow QRS may actually have dyssynchrony. This may explain why a substantial fraction of patients with wide QRS are non-responders to CRT in the large trials.
A number of echocardiographic indices have been proposed as markers of success of CRT. However, when tested against QRS width in prospective clinical trials, none of the echocardiographic indices are proven to give clinical benefit in patient selection for CRT. Although QRS duration is an imperfect marker of responders to CRT, there is yet no other consensus definition of dysynchrony that has been sufficiently evaluated. Therefore, current international guidelines do not recommend routine quantitation of dysynchrony by echocardiography in the evaluation of patients who are considered potential candidates for CRT. The value of using QRS width as a selection criterion is best documented in patients with QRS width ≥150 ms who have the greatest benefit from CRT. In patients with a QRS width of 120–150, results from CRT are more variable.

Assessment of inter-ventricular dyssynchrony

Inter-ventricular dyssynchrony is measured by Doppler echocardiography as the difference between LV and right ventricular pre-ejection intervals calculated from the onset of QRS on ECG to the onset of aortic outflow and pulmonary outflow, respectively. It has been shown that reversed LV remodelling and improved LV function during CRT is associated with a reduction in inter-ventricular dyssynchrony. However, most evidence suggests that inter-ventricular dyssynchrony is not as useful in the prediction of response to CRT as LV intra-ventricular dyssynchrony.

Assessment of left ventricular intra-ventricular dyssynchrony

Two-dimensional and M-mode echocardiography

The initial step in the assessment of intra-ventricular dyssynchrony should be conventional grey-scale two-dimensional (2D) imaging and one should look for abnormal septal motion. Objective evidence of abnormal septal motion can be obtained by M-mode echocardiography which in typical cases shows rapid pre-ejection leftward motion of the septum, followed by rightward motion, a pattern which is named septal beaking. This phenomenon can also be observed by tissue Doppler and is then named ‘septal flash’ (Figure 1). Although present only in some patients with LBBB, septal flash has shown to be a good predictor of response to CRT both in terms of clinical response and reverse remodelling. Another abnormal motion pattern which is consistent with significant LV intraventricular dyssynchrony is apical rocking. In addition to these qualitative methods, a number of quantitative echocardiographic measures of dyssynchrony are available.

The technically simplest approach to quantify LV dyssynchrony is septal-to-posterior wall motion delay by conventional M-mode echocardiography in the parasternal short-axis view. This method may work in patients with non-ischaemic cardiomyopathy, but is more difficult to apply in ischaemic cardiomyopathy, since previous infarcts and akinesia in the measurement regions make it difficult to define the peaks of septal and posterior wall inward motion.

Tissue Doppler velocity imaging and speckle-tracking strain imaging

Velocity imaging by tissue Doppler and strain imaging by speckle-tracking echocardiography (STE) have been the preferred echocardiographic methods to quantify mechanical dyssynchrony. A detailed description of the procedure is found in a consensus statement from the American Society of Echocardiography. One approach is to assess velocities in the basal part of six basal and six mid-LV segments, and to measure time from beginning of the QRS signal to ‘peak’ systolic velocity during LV ejection (Figure 2). Regional differences in time to peak systolic velocity can be expressed as standard deviation for measurements from all 12 segments and has been shown to predict reverse remodelling in a number of smaller studies with CRT. Maximal delay in peak velocity between the anterior, inferior, septal, and lateral walls has also been shown to
predict clinical response to CRT and reverse remodelling.\textsuperscript{25,26} As discussed later in this article, the principle of using ejection-phase velocities to identify candidates for CRT may not be optimal and may even be misleading. A recent article addressed this limitation of ejection-phase velocities.\textsuperscript{28} The issue about validity of using ejection-phase velocities is essential to resolve since several trials, including the negative PROSPECT trial,\textsuperscript{13} used myocardial ejection velocities to quantify dyssynchrony. Recent studies suggest that timing of peak strain may be a more useful measure of dyssynchrony when evaluating patients for CRT.\textsuperscript{29–31} A study which tested most of the proposed echocardiographic indices, however, concluded that none of the current indices predicted clinical response to CRT.\textsuperscript{14}

**Future directions**

As discussed in the subsequent paragraphs, one reason for the apparent failure of echocardiography to provide added value in selection of patients for CRT may be that suboptimal methodological approaches have been used. In particular, lack of methodology to differentiate between electrical and non-electrical aetiologies of dyssynchrony is important since it is primarily dyssynchrony caused by electrical conduction delay which will respond to CRT. Furthermore, the use of ejection-phase velocity indices may have confused the issue because peak ejection velocity has significant limitations as a marker of electrical conduction delay. In addition, there is a need for better standardization of measurement techniques. Therefore, it may be too early to conclude about the diagnostic value of echocardiography in selection of candidates for CRT.

In the following paragraphs, we will take a critical look at some of the principles behind current echocardiographic methods and we propose new diagnostic approaches which may be worth exploring.

**Differentiation between electrical and non-electrical causes of dyssynchrony**

Dyssynchrony is defined as uncoordinated regional myocardial contractions\textsuperscript{12} and may in principle have three different aetiologies: (i) electrical conduction delay which causes non-uniform timing of myocyte depolarization (i.e. ‘primary electrical dyssynchrony’), (ii) abnormalities in excitation–contraction coupling, and (iii) abnormal myocardial contractility or load which cause regional delay in onset shortening and in time to peak shortening (i.e. ‘primary mechanical dyssynchrony’). Primary electrical dyssynchrony is

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**Figure 2** Colour-coded tissue Doppler study from three standard apical views of a patient who responded to resynchronization therapy. Pre-treatment time–velocity curves from representative basal or mid-levels are shown. Maximum opposing wall delay (of peak ejection velocity) was seen in an apical long-axis view of 140 ms between the septum and posterior wall, consistent with significant dyssynchrony (\(>65\) ms). AVC = aortic valve closure; AVO = aortic valve opening. Gorcsan et al.\textsuperscript{12}

**Figure 3** (Left panel) Definition of onset active force generation: recordings from a dog model in which onset active force generation was defined as the time of upward shift from segmental passive-elastic curve. (Right panels) Onset active force generation in the left ventricular lateral wall and septum in a patient with left bundle branch block. Onset of active force generation defined as the time that corresponded to the first marked upward deviation of the pressure-strain loop that resulted in a continued upward shift (circle). AFG = Active force generation.
use. One disadvantage is that invasive pressure is needed. Patients
who are candidates for CRT, however, often need left heart cath-
ereterization and this provides access to LV pressure.

We have recently introduced a novel, non-invasive method to
measure LV pressure-strain loops which might have a potential
to identify electrical dysynchrony. The method is described in
more detail in the last section of this article. As illustrated in
Figure 4, regional LV pressure-strain loops are entirely different
for segments with electrical dysynchrony when compared with
segments with reduced contractility due to ischaemia, although
loop area and therefore segmental work is reduced in both
cases. The most characteristic feature of electrical dysynchrony
is that the early-activated septum has marked pre-ejection shorten-
ing accompanied by pre-ejection lengthening in the lateral wall. An
ischaemic segment, however, has typically pre-ejection lengthening
and there is no associated pre-ejection lengthening in the opposite
wall. It remains to be explored if pressure-strain loop configura-
tions may be used this way to identify electrical dysynchrony.

Correct timing of septal activation

In patients with electrical dysynchrony, the septum is usually
activated first and timing of LV free wall activation is made
with reference to the septum. It is therefore critical that timing
of septal activation is done properly. Due to complex septal de-
formation patterns in LBBB, it is challenging to define the mech-
nanical event which best reflects timing of septal activation. In
normal hearts, the septum, similar to the LV free wall, shortens
continuously during the LV ejection phase. During LBBB,
however, septal deformation has two phases of systolic shorten-
ing, each followed by systolic lengthening as illustrated in
Figures 5 and 6. Furthermore, as shown by Leenders et al.,
this strain pattern may be modified by changes in contractility
in the septum or LV free wall.

The study of Gjesdal et al. suggests that onset of pre-ejection
septal shortening rather than onset of ejection shortening should
be used for timing of septal activation. This is supported by the
observation that onset R in local EMG coincides with the onset
of septal shortening (Figure 6). Furthermore, the observation that
pre-ejection septal shortening occurs against rising LV pressure is
consistent with active septal contraction and implies that the
septum is electrically activated during the pre-ejection phase
(Figures 3, patient, and 4, experimental).

Myocardial ejection velocities
in assessment of dyssynchrony

Clinical studies which have investigated the ability of tissue
Doppler echocardiography to identify responders to CRT have
often measured peak myocardial velocity during LV ejection. This
was also done in the PROSPECT-trial which concluded that no
echocardiographic measure of dyssynchrony may be recom-
mended to improve patient selection for CRT. As discussed in
the previous paragraph of this article and as suggested by the
studies of Russell et al. and Gjesdal et al., ejection-phase veloc-
ties may be suboptimal measures of electrical dysynchrony. There
is no doubt that differences in timing of peak myocardial shortening
velocity reflect mechanical dysynchrony, but there are little data

Figure 4 (A) Left ventricular pressure-strain loops during left bundle branch block from a dog experiment measured in the LV lateral wall and in the septum. In the lateral segment, the pressure-strain loop rotates counterclockwise, which is the normal pattern, and the area of the loop reflects segmental work. In the septal segment, loop area is markedly reduced relative to the lateral segment, which implies that septal work is markedly reduced. Part of the septal pressure-strain loop rotates clockwise, which means that work is performed on the septum by other segments. The septal loop also illustrates that pre-ejection septal shortening (red arrow) is active since it occurs against rising left ventricular pressure. (B) Left ventricular pressure-strain loops during left anterior descending coronary artery occlusion. The anterior segment is stretched in systole and the loop area is almost zero, indicating that the segment is affected by ischaemia and is not generating work. The black circle indicates the onset of active myocardial force generation.

typical for LBBB and primary mechanical dyssynchrony is typical for
regional ischaemia. The electrical and non-electrical aetiologies of
dyssynchrony need to be differentiated since delay in electrical
conduction may be the only aetiology amenable for CRT. We
believe that clear differentiation between aetiologies is essential
for understanding and applying dyssynchrony indices.

We recently introduced a novel method to estimate timing of
electrical activation and thereby identify electrical dyssynchrony. This method utilizes LV pressure-strain loops to measure onset of
active myocardial force generation (AFG). In an experimental prep-
aration with implanted myocardial electrodes, we could show that
time differences in onset AFG tracked very well regional differ-
ences in onset electrical activation since excitation–contraction
coupling time was essentially constant. This was confirmed
during different haemodynamic conditions, myocardial ischaemia,
and LBBB. Figure 3 shows how to measure onset AFG. So far,
the AFG method has only been used for research purposes and
further testing is needed before it can be recommended for clinical
to support a strong relationship to electrical dyssynchrony. Figure 7, which is from an experimental study, illustrates how differences in timing of peak ejection velocity may lead to wrong conclusions regarding electrical dyssynchrony. It shows that peak septal ejection velocity occurs after peak lateral wall velocity during LBBB, whereas EMG by myocardial electrodes confirms

**Figure 5** Systolic strain traces from the septum (thick lines) and lateral wall (thin lines) in a patient with left bundle branch block before (left) and after treatment with cardiac resynchronization therapy (right). During left bundle branch block without cardiac resynchronization therapy, there is a marked septal shortening during pre-ejection and there is shortening during mid-ejection (red). Each shortening is followed by lengthening, resulting in both early- and late-systolic lengthening (blue). The lateral wall shows pre-ejection lengthening before treatment (green). These changes are reverted after treatment. A pre-ejection stretch has appeared in the septum after treatment with cardiac resynchronization therapy, indicating that there is slight dyssynchrony also during cardiac resynchronization therapy. AVC = aortic valve closure; AVO = aortic valve opening; MVC = mitral valve closure; MVO = mitral valve opening. Modified from De Boeck et al.14

**Figure 6** Pressures, septal segment length by sonomicrometry, septal intramyocardial electromyogram (EMG), and electrocardiogram (ECG) in a dog with left bundle branch block. The first vertical line indicates timing of electrical activation of the septum as measured by EMG. The next vertical lines indicate timing of aortic valve opening (AVO) and closure (AVC). There are two phases of septal systolic shortening and relengthening. Please note that onset septal shortening during ejection does not correspond to timing of electrical activation of the septum as measured by EMG. ED = end diastole.

**Figure 7** Representative traces from an experimental study showing velocity by sonomicrometry and regional electrical activation by intramyocardial electromyograms (EMG) for a septal and lateral LV wall segment during left bundle branch block. Note that peak septal ejection velocity occurs after peak lateral wall velocity, opposite to electrical activation by intramyocardial EMGs. AVC = aortic valve closure; AVO = aortic valve opening; IVC = isovolumic contraction.
that the septum is activated first. As they are yet not sufficiently proven to work, we suggest that ejection-phase velocities are not applied as standalone markers of electrical dyssynchrony in relation to CRT.

**Peak myocardial strain as a marker of dyssynchrony**

As discussed above, recent studies indicate that myocardial strain may be superior to velocities for evaluation of dyssynchrony. Due to complex mechanical interactions between different parts of the LV wall, strain traces also need to be interpreted with caution. This limitation is illustrated by the two clinical examples in Figure 8. In Patient 1, different timing of peak strain in septum and LV lateral wall suggests marked dyssynchrony, whereas Patient 2 apparently has no significant dyssynchrony. Both patients have LBBB with QRS width >150 ms and no known coronary artery disease. In these circumstances, we would argue that it is highly unlikely for the septum to be activated after the lateral wall as suggested by timing of peak strain for Patient 2. This probably reflects dependency of timing of peak strain on other factors than electrical conduction.35

Experimental studies suggest that strain derived dyssynchrony indices may exaggerate underlying electrical dyssynchrony. Prinzen et al.38 have shown that delay in onset shortening between early and late activated LV segments exceeds the delay in electrical conduction during pacing-induced dyssynchrony. In a recent study,38 we showed that the apparent electromechanical delay in the LV lateral wall during LBBB is due to higher rate of LV pressure rise (due to early septal contraction) at the time of lateral wall activation, resulting in a longer time before the segment generates active force at a rate superior to the load rise which is a requirement for shortening. These findings suggest that LV contractility may modify timing of onset of shortening and hence mechanical dyssynchrony.

**Assessing regional work: a new approach for understanding dyssynchrony**

LV dyssynchrony is associated with marked inter-segment differences in myocardial work27 as illustrated in Figures 3, right panel, and 4. During LBBB, the septum performs little and in some cases negative work, whereas the LV lateral wall is hyperactive due to pre-systolic stretching (increased preload) caused by the early-activated septum (Figure 4). Analysis of regional work during electrical dyssynchrony may provide important insights into mechanisms of remodelling and LV dysfunction.37,39,40 Abnormal inter-segmental work distribution during LBBB is associated with differences in regional blood flow and oxygen demand and may also account for remodelling of the LV with hypertrophy of the hyperactive LV lateral wall and thinning of the early-activated septum.40–43

We have recently introduced a non-invasive method to assess regional myocardial work by LV pressure-strain loops analysis.44 A non-invasive LV pressure is obtained by using an empiric, normalized reference curve which is adjusted according to duration of the isovolumic and ejection phases determined by echocardiography, and absolute pressure level is estimated from brachial artery cuff pressure. The non-invasive LV pressure-strain loop area gives an accurate quantification of regional work when using invasive LV pressure-strain loops as the reference method.44 and the method
is currently undergoing clinical testing. Assessment of regional work may provide important insights into cardiac mechanics and may be useful when evaluating patients who are candidates for CRT.

Concluding remarks

There is no doubt that echocardiography represents a unique tool for quantification of LV dyssynchrony, but further studies are needed before a conclusion can be reached regarding its role in selection of patients for CRT. We recommend that new developments focus on methods that can differentiate between electrical and non-electrical aetiologies of dyssynchrony and on methods to quantify its negative mechanical impact. Ultimately, only patients with an electrical aetiology are likely to respond favourably to CRT. Just measuring velocity indices does not identify the aetiology. Myocardial strain appears more promising, but one should be aware that timing of peak systolic strain is determined not only by electrical conduction. One should also take into account potential ischaemia, scarring, and other structural changes as contributors to dyssynchrony. The proposed AFG method to identify electrical dyssynchrony and LV pressure-strain loop analysis to quantify the impact of dyssynchrony on regional work may be worth exploring in future studies. Furthermore, it is important to be aware that LV dyssynchrony may have a combination of aetiologies, not all amenable for CRT.

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