ECHOCARDIOGRAPHIC METHODS TO SELECT CANDIDATES FOR CARDIAC RESYNCHRONISATION THERAPY

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The observation that heart failure with reduced ejection fraction is often accompanied by asynchronous contraction of the left ventricle, leading to a loss of mechanical efficiency in ejection and an increase in mitral regurgitation, has prompted the development of cardiac resynchronisation therapy (CRT) as a therapeutic option in symptomatic heart failure. This technique, based on pacing the left ventricle, both ventricles, or both ventricles and the right atrium, has now been shown in randomised trials to reduce morbidity and hospitalisations[1] and to decrease mortality[2] in symptomatic patients with reduced ejection fraction and a QRS width of 120 ms or more. In these studies, the width of the QRS complex has been used as a surrogate for cardiac mechanical asynchrony. However, following current guidelines to identify candidates, about a quarter of patients treated by CRT will lack improvement or even deteriorate (''non-responders''). On the other hand, the proportion of heart failure patients who might benefit but who are not covered by current indications is unknown. Substantial left ventricular asynchrony has been documented in patients with congestive heart failure and normal QRS duration,[3 4] suggesting that some of these patients might respond to CRT. Thus, a better way to select CRT candidates is needed to optimise the application of this costly therapy. While current guidelines base their criteria largely on clinical and ECG criteria,[5] echocardiography is particularly promising, because this technique directly evaluates mechanical (as opposed to electrical) asynchrony with high temporal and spatial resolution.

Conceptually, cardiac asynchrony can be divided into atrioventricular, interventricular, and intraventricular asynchrony (of the left ventricle), the latter being widely regarded as the most important component.

ATRIOVENTRICULAR ASYNCHRONY

A long atrioventricular interval (time interval from atrial to ventricular excitation or contraction) is detrimental in heart failure because: (1) early passive diastolic filling time is reduced; (2) atrial systole may coincide with early filling, thereby decreasing the effectiveness of the atrial booster pump; and (3) late diastolic mitral regurgitation may occur. Identification of the optimal time delay between atrial and ventricular pacing can be aided by Doppler echocardiography of transmitral inflow. Typically, the minimal atrioventricular pacing delay is selected that is still long enough to avoid truncation of the transmitral A wave by the onset of ejection.[6] However, rigorous proof of the effectiveness of this principle is lacking and its use has been questioned for a subset of patients with heart failure and ventricular conduction delay, for whom the haemodynamically optimal atrioventricular delay may be shorter than the one defined by ensuring full A wave duration on the transmitral flow profile.[7]

INTERVENTRICULAR ASYNCHRONY

The time delay between left and right ventricular ejection can be assessed by comparing the timing of onset of flow in the right and left outflow tracts by pulsed Doppler with respect to the ECG. A delay of 40 ms or more, with the left ventricle trailing the right, is considered sufficiently large to support interventricular resynchronisation by appropriate left ventricular or biventricular pacing. Alternatively, the time to peak systolic tissue velocity in the basal right ventricular free wall has been compared to the basal lateral left ventricular wall as a measure of interventricular synchrony. Simultaneous biventricular pacing was reported to abolish the interventricular delay.[8] Another study, however, reported that sequential pacing of the left and right ventricle is superior to simultaneous biventricular pacing.[9] In this study, eight of nine patients with dilated cardiomyopathy had predominantly a lateral left ventricular delay in mechanical activation, while 10 of 11 patients with ischaemic cardiomyopathy had predominantly a septal and inferior activation delay; all had left bundle branch block with a QRS duration over 130 ms. Patients with lateral activation delay benefited most from pacing first the left and then the right ventricle, while patients with inferoseptal delay were best paced first in the right and then in the left ventricle, with optimal activation intervals of only 12–20 ms.

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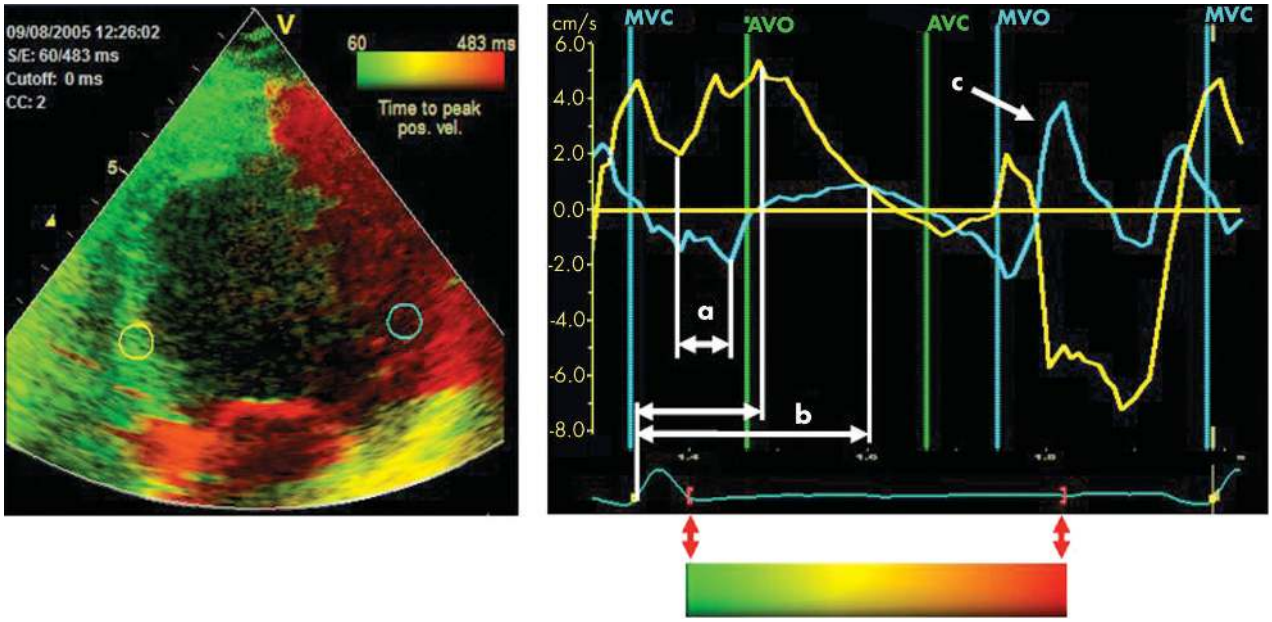

Figure 1 Examples of parameters suggested in the literature to identify potential cardiac resynchronisation therapy (CRT) responders. Representative tracing obtained from the apical four chamber view in a patient with dilated cardiomyopathy and left bundle branch block (left). Colour coding in ''tissue synchronisation mode'' (left image) displays the time from the onset of QRS complex to peak positive tissue velocity. The interval which is colour coded (here 60–483 ms) is adjustable; for illustration purposes, the colour bar has also been transferred to the time scale of the spectral tissue Doppler display (right image). Green colour codes for early and red colour for late peak tissue velocity. Right image: tissue velocity recordings from the basal septal (yellow) and basal lateral (cyan) segment. Arrow ''a'' denotes the time difference in onset of positive (apically directed) myocardial velocity between septum and lateral wall (62 ms). Arrows ''b'' denote the time to peak systolic velocity in the two walls, with a difference of 121 ms. ''c'' points at ''post-systolic contraction'' occurring after mitral valve opening, or, more correctly, a post-systolic apically directed velocity peak. See text for further details. AVC, aortic valve closure; AVO, aortic valve opening; MVC, mitral valve closure; MVO, mitral valve opening.

INTRAVENTRICULAR ASYNCHRONY

Intraventricular asynchrony appears to be the most important factor for the success of CRT. The principle is to identify the longest regional delay in mechanical activity and to realign it with the rest (or largest part) of the ventricle by pacing. In the typical left bundle branch block patient, the septum is depolarised via the right bundle branch well before the depolarisation wavefront reaches the lateral or posterior wall, and this asynchrony in depolarisation produces asynchronous contraction. Initially, the delay between anteroseptal wall contraction and posterior wall contraction has been assessed by M mode echocardiography, and a cut-off of 130 ms was found predictive of CRT benefit.[10] However, in severely depressed ventricles and dyskinetic left ventricular walls, identification of timing of active contraction on M mode recordings is frequently impossible, and especially in ischaemic cardiomyopathy, contraction patterns often are more complicated. Even segments of the same wall may exhibit asynchrony relative to each other.

Several newer approaches to assessing left ventricular asynchrony and predicting CRT response have been proposed and examined over recent years. Tissue Doppler, which measures tissue motion velocity, and its derived modality, deformation imaging, which measures regional strain and strain rate, are able to determine timing and extent of left ventricular mechanical events with good spatial and very high temporal resolution. While initial studies have used pulsed tissue Doppler, acquisition of colour coded maps of tissue velocities is faster and more convenient, since the velocity information from different segments and walls can be recorded in the same cine loop. Another novel echo technique, three dimensional (3D) echocardiography, allows comprehensive evaluation of the timing of endocardial motion of all ventricular segments from one 3D dataset.

NEWER ECHO PARAMETERS OF LEFT VENTRICULAR ASYNCHRONY

The standard deviation of the time from onset of QRS to peak systolic tissue velocity of the basal and mid segments of all six left ventricular walls is shown in fig 1.[11] A cut-off of 33 ms has predicted mechanical benefit from CRT. In a recently published head-to-head comparison of the predictive power of several tissue Doppler parameters, this parameter had the best predictive power.[12] This approach has been taken further by automatically colour coding segments according to their time to peak systolic tissue velocity (''tissue synchronisation imaging'' and similar parametric imaging modalities from different manufacturers) for easier detection (figs 1–3). The colour map can be used for rapid visual identification of late moving segments, which then should be supplemented by detailed analysis of curves from different segments.

A similar, but simplified approach using only the difference in time to peak between the basal septum and basal lateral wall segment in the apical four chamber view has also been used recently.[13 14] A septal to lateral delay of 65 ms or more in time to peak tissue velocity predicted improvement in left ventricular ejection fraction and clinical symptoms.[15 16]

Presence of post-systolic (that is, after aortic valve closure) positive tissue velocities or shortening on strain/strain rate recordings, labelled ''delayed longitudinal contraction'', is shown in fig 4.[9 12 17]

Another newer echo parameter is comparison of timing of strain and strain rate curves from different left ventricular regions. These data, which are derived from tissue velocity data,

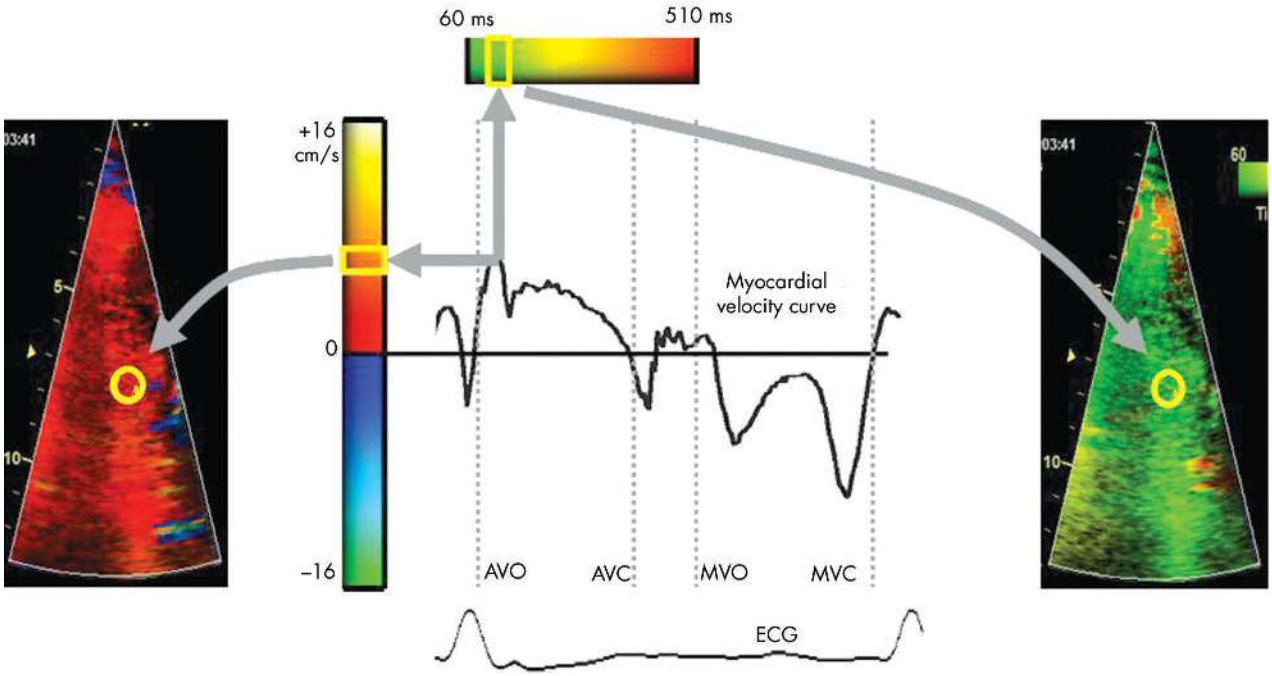

Figure 2 Comparison of different parametric (colour coded) imaging modalities based on myocardial velocities: tissue velocity imaging (TVI, left) and tissue synchronicity imaging (TSI, right). Both recordings are from a normal septal segment. In TVI, the velocity of the myocardium (amplitude of the tissue velocity curve; here 8 cm/s) is colour coded. TSI displays the timing of the velocity peak relative to the onset of QRS in the ECG within a given interval (here 60 ms).

are often noisy and more difficult to interpret than tissue velocity data. They are, however, less subject to translation artefacts and tethering of adjacent structures. One study has directly compared the utility of tissue velocity measurements (in particular, the standard deviation of regional time to peak tissue velocities) to regional strain rate measurements or the presence of post-systolic positive tissue velocity.[18] These authors found tissue velocity parameters to provide better discriminatory power than strain rate parameters, although this conclusion has not been universally accepted.

Another newer technique is timing of regional left ventricular inward motion of endocardium by 3D echocardiography and semi-automated boundary detection.[19] This technique uses real-time 3D echo to acquire a three dimensional dataset of the left ventricle throughout a cardiac cycle. From these data, with the use of a semi-automated endocardial boundary recognition algorithm, regional filling curves are derived for left ventricular myocardial segments, and the timing of these curves is compared to visualise ventricular asynchrony (fig 5).

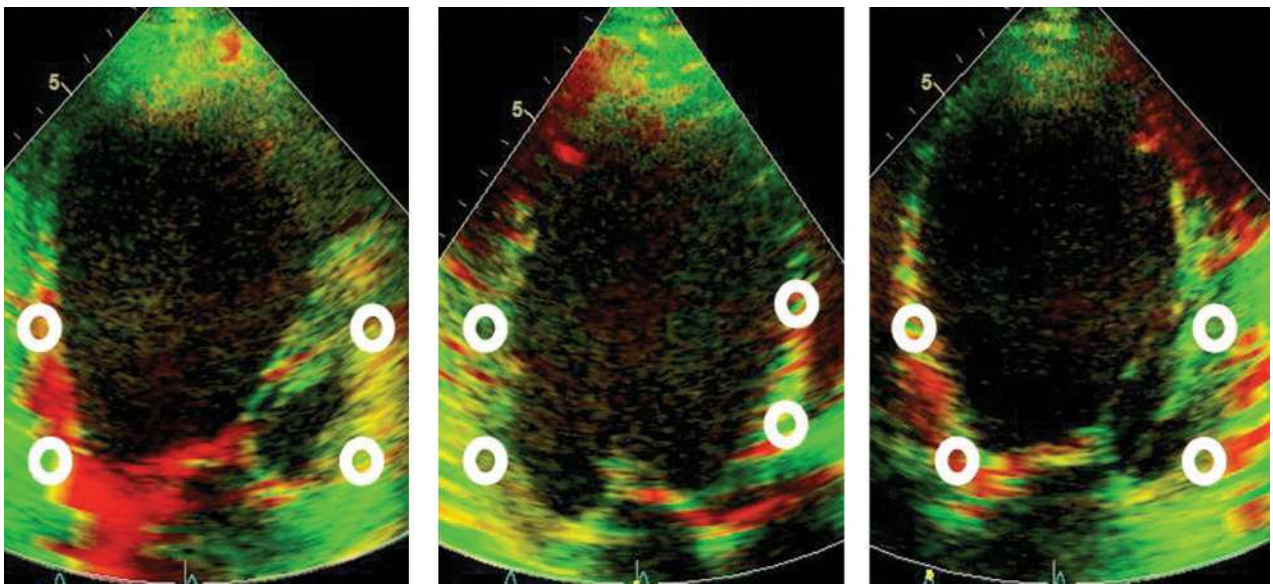

Figure 3 Apical four chamber, apical long axis, and apical two chamber view in ''tissue synchronisation imaging'' mode. Circles indicate the typical 12 sampling positions to determine the standard deviation of time to peak velocity.[14]

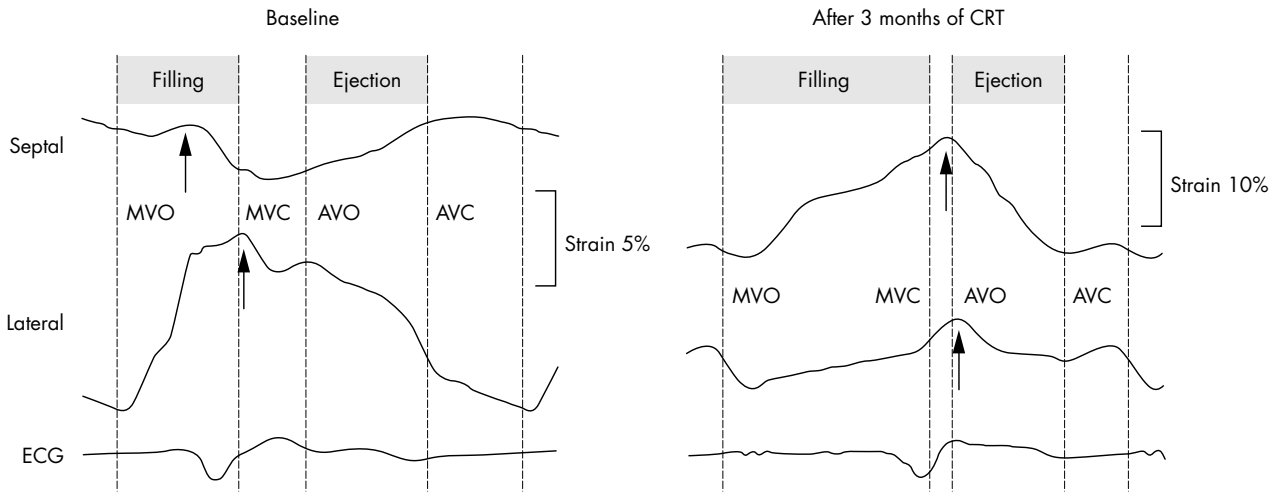

Figure 4 Effect of CRT assessed by strain curves. Mid septal and mid lateral strain before (left) and three months after institution of CRT (right). Left: note the asynchronous onset of myocardial shortening (arrows) which results in a shortened diastolic filling period, septal lengthening during ejection time and, thus, inefficient left ventricular pump function. The time interval between lateral and septal onset of shortening is 63 ms. Right: striking alignment of septal and lateral strain curves under CRT.

LIMITATIONS OF PRESENT METHODS

At the present time none of these criteria has been evaluated in a large number of patients, or with respect to clinical outcomes. In particular, in all studies the indication for CRT treatment was based mainly on non-echocardiographic, clinical criteria. Benefit from CRT has been assessed by an increase in left ventricular ejection fraction, a decrease in left ventricular volumes, and by clinical indicators such as functional class or the six minute walk test, but not by long term clinical outcomes.

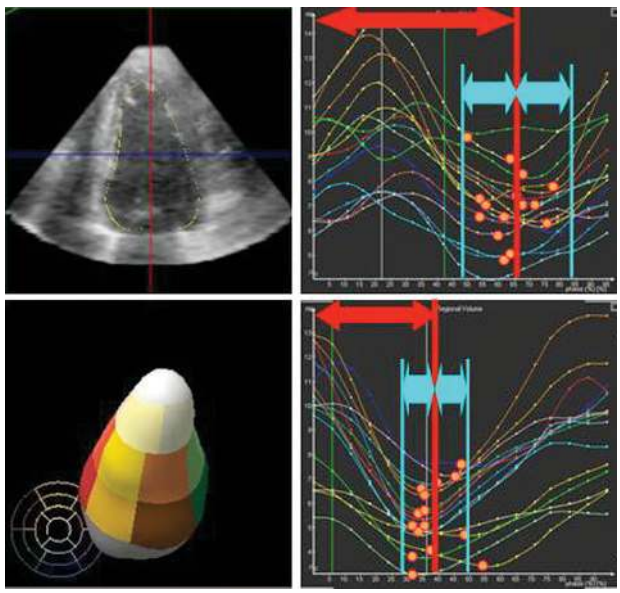

Figure 5 Assessment of left ventricular asynchrony by real time, 3D echocardiography. Top left: real time 3D echo dataset cut to display a four chamber view with semiautomatic endocardial border tracing. Bottom left: representation (''cast'') of left ventricle produced by multiple semiautomatic border tracings in the 3D dataset. Segments are marked with different colours. Top right: regional filling curves from pyramidal volume components of the left ventricular cavity, each pyramidal volume component corresponding to a left ventricular segment. The curves are derived from a patient with severe asynchrony and heart failure before CRT. There is wide variation in the timing of regional minimal volume. The arrows denote mean and standard deviation of time to regional minimal volume. Bottom right: after institution of CRT, mechanical synchrony is improved. Courtesy of Dr Andreas Franke, Aachen, Germany.

A fundamental methodological limitation of current Doppler methods is that velocity and, even more so, strain and strain rate are prone to angle related errors. Most researchers have therefore only assessed longitudinal (long axis) velocities and contraction patterns. However, angle correction tools and two dimensional strain measurement are being implemented in echocardiographic machines and will allow further refinement in the future.

Neither tissue velocity imaging nor strain/strain rate imaging can distinguish active from passive motion (for example, active shortening from passive recoil after previous stretching). Thus, areas of ''delayed contraction'' may simply represent scar tissue and not contain contractile myocardium, and thus not benefit from resynchronisation.

Furthermore, theoretically not only the timing of tissue velocities matters but also the actual extent of tissue displacement, because this displacement corresponds to the amount of blood propelled and thus to mechanical efficiency. This displacement is not only related to the timing of peak velocity, but also to the integral of tissue velocities and to the amount of tissue participating in this motion. For example, a small left ventricular region with a short late peak in systolic tissue velocity should have less impact on overall ejection efficiency than a larger region exhibiting a more prolonged rise in systolic tissue velocity, although both may have the same time to peak systolic velocity or may both show post-systolic motion.

''Tissue synchronisation imaging'' and similar colour coding algorithms are very sensitive to the settings of the time window within which the algorithm searches for the peak positive tissue velocity. This window defaults to an interval derived from the ECG signal, which may or may not accurately represent left ventricular ejection. Its use should therefore always be checked against the actual timing of valvar events, in particular aortic valve closure (compare figs 1 and 2).

Several heart failure patient groups might benefit from CRT who are not covered by current implantation guidelines[5]—patients with right bundle branch block, patients with QRS width under 120 ms, or patients in atrial fibrillation. For these groups some encouraging data exist, but a uniform recommendation cannot be made at present. It is likely that particularly in these patients echocardiographic evidence of mechanical asynchrony will be important to select proper candidates for CRT.

A CONTEMPORARY APPROACH TO ECHO ANALYSIS OF LEFT VENTRICULAR ASYNCHRONY

The following recommendations are based on the authors' practice and represent no claim to superiority to other methodologies. They are intended to maximise the likelihood that candidates will actually profit from CRT, not to maximise the number of candidates.

First, look qualitatively at the ventricle in parasternal short axis and apical (especially four chamber) views. The aspect of a swinging left ventricle shifting blood from one side to the other instead of ejecting it is often striking. We are hesitant to recommend CRT if no such swinging is seen. However, swinging is often induced by the presence of large areas of scarred myocardium with dyskinetic motion, which may not be responsive to pacing.

Second, note whether the segment analysed is still thickening or most likely scar moving passively by tethering from adjacent segments. In the latter case, benefit from pacing is unlikely.

Third, record tissue velocities and strain profiles from segments of two opposite walls at approximately the same level (that is, basal or mid) in an apical view—for example, septum and lateral wall in the four chamber view—and compare their phase qualitatively (that is, look how well shortening and lengthening match). To ensure that timing is accurate, the curves from the two sites should be extracted from the same cycle and view. If a colour map is used for first orientation (for example, ''tissue synchronisation imaging''), findings should be confirmed by analysing velocity or deformation curves over time from individual segments. During recording of velocity or strain/strain rate data, the following points must be observed:

- a frame rate well over 100/s should be obtained
- angle errors must be carefully minimised
- a reproducible signal with as little beat-to-beat variation as possible should be sought; ideally, electronic averaging of several beats is advisable
- opening and closing of the aortic and mitral valve should be recorded and implemented into the display of velocity or deformation over time (compare figs 1 and 4).

A delay of at least 60–80 ms between curves from opposite segments, which is reproducible at multiple sample volume locations, and ideally detectable both in tissue velocity (for example, as time difference between peak systolic velocities) as well as strain rate curves (for example, as time difference between the onsets of shortening (fig 4)), would favour CRT, particularly if curves from opposite walls show contrary direction of deformation during ejection—for example, lateral wall shortening during septal wall lengthening. Whether tissue velocity curves, tissue synchronisation imaging, strain, or strain rate curves are better suited for decision making is unresolved. It is likely, however, that there is not a single parameter or cut-off value allowing a clear cut decision about whether a patient should receive CRT or not, and all available information should therefore be weighed when making this decision.

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