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Assessment of apical rocking: a new, integrative approach for selection of candidates for cardiac resynchronization therapy

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Aims Current attempts of improving patient selection in cardiac resynchronization therapy (CRT) are mainly based on echocardiographic timing of myocardial velocity peaks. Regional myocardial function is neglected. Apical transverse motion (ATM) is a new parameter to quantify apical rocking as an integrative surrogate of both temporal and functional inhomogeneities within the left ventricle. In this study, we tested the predictive value of apical rocking for response to CRT.

Methods and results Sixty-nine patients eligible for CRT were assessed by echocardiography before and 11 ± 5 months after pacemaker implantation. Response was defined as left ventricular (LV) end-systolic volume decrease >15%. Rocking was quantified (ATM) and visually assessed by four blinded readers. Predictive value for CRT response of both assessments was compared with conventional dyssynchrony parameters. ATM in the four-chamber view plane differentiated best between responders and non-responders (2.2 ± 1.5 vs. 0.06 ± 1.9 mm, $P < 0.0001$). Quantified ATM predicted reverse remodelling with a sensitivity, specificity, and accuracy of 75, 96, and 83% whereas visual rocking assessment resulted in 89, 75, and 83%, respectively. The accuracy of conventional parameters was significantly lower.

Conclusion Apical rocking is a new marker to assess LV dyssynchrony and predict CRT response. It is superior to conventional parameters. Even its simple visual assessment may be sufficiently accurate in the clinical setting.

Keywords Echocardiography • Heart failure • Pacing • Remodelling • Cardiac resynchronization

Introduction

Cardiac resynchronization therapy (CRT) has become an established treatment option for patients with heart failure and conduction delays.[1] According to current guidelines, patient candidate selection for this costly therapy relies mainly on clinical criteria, ejection fraction (EF), and QRS width, and results in a non-response rate in the range of 30%.[1]

Since CRT aims to re-synchronize left ventricular (LV) mechanical contraction,[2] a proof of mechanical instead of electrical dyssynchrony[3] supported by the evaluation of remaining myocardial function[4,5] may allow better patient selection.

For both, echocardiography appears as method of choice. It is widely available and has the potential to image and quantify regional function with good spatial and excellent temporal resolution. Two questions have to be answered during a dyssynchrony assessment: (1) 'Is there a temporal inhomogeneity in regional myocardial contraction?' and (2) 'Is there a regional inhomogeneity in the residual myocardial function?'. Although the first question appears easy to answer, the second is challenging because of the marked functional interaction of myocardial regions during the cardiac cycle.

Several parameters have been suggested for the assessment of LV dyssynchrony, most of which are based on the analysis of

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timing of longitudinal myocardial velocity peaks.[6] These parameters allow, to a certain degree, the assessment of timing inhomogeneities within the LV (answering question 1). However, interaction between regions (tethering) does not allow the measurement of true regional function on this basis (question 2).[7] Accordingly, recent publications have raised doubts about the robustness and predictive value of peak-velocity-based parameters in a routine clinical setting.[8]

We have developed a completely new approach to assess LV mechanical dyssynchrony by analysing apical rocking. Apical rocking is the mechanical result of both timing and function inhomogeneities within the LV.[9–11] It may be quantified with the simple parameter of Apical Transverse Motion (ATM)[9] or may be visually assessed. This study was set up to test the ability of apical rocking to predict reverse remodelling in CRT candidates. Furthermore, we tested if the visual assessment of 'apical rocking' is a feasible tool to predict response to CRT in a clinical setting.

Methods

Study population and protocol

The study group comprised 69 heart failure patients (mean age 63 ± 10 years; 53 males) eligible for CRT according to current guideline criteria. Ischaemic origin of heart failure was proved by coronary angiography and/or records of myocardial infarction in 36 (52%) of the patients. At the time of inclusion, none of the candidates required interventional or surgical treatment for coronary disease. All patients were in sinus rhythm and on optimized pharmacologic therapy for at least 3 months before CRT. None had more than mild valvular disease.

Biventricular pacing systems were implanted. LV pacing leads were positioned, guided by coronary venography, in lateral and posterolateral venous branches. Device settings were optimized on the third day based on surface ECG and Doppler echocardiography.[1,12,13]

Follow-up time was 10.7 ± 5.5 months. Patients with a LV end-systolic volume (ESV) decrease >15% during follow-up were regarded as responders.[14–16]

All patients gave written informed consent prior to inclusion.

Echocardiographic data acquisition

Standard two-dimensional and Doppler echocardiography was performed using Vivid 5 and Vivid 7 ultrasound scanners (GE Vingmed, Horten, Norway). Tissue Doppler data were acquired in apical 2-, 3-, and 4-chamber views (A2C, A3C, and A4C, respectively). Depth and sector angle were adjusted in order to maximize frame rate (typically 110 frames/s). Image loops of three consecutive beats were digitally stored for further off-line analysis. Spectral flow Doppler derived timing of valve openings and closures was used to define cardiac time intervals.

Post-processing

An EchoPAC workstation (software version 7.0.1, GE Vingmed Ultrasound, Horten, Norway) was used to measure LV dimensions and volumes (biplane Simpson's method) and to extract myocardial Doppler velocity traces from all apical, mid, and basal segments of all six LV walls. Sampling regions were tracked during the cardiac cycle in order to achieve a constant midwall position. Velocity traces were numerically stored and further post-processed using dedicated, MATLAB-based (version 2006a, The MathWorks, Inc., Natick, MA, USA) research software (TVA version 14.3, JU Voigt, Leuven).

Apical transverse motion calculation

The principle of quantifying LV apical rocking by measuring ATM is described elsewhere.[9] In short, the apex is considered a 'cap' with homogeneous material properties on which the different walls are pulling. ATM, defined as the apex motion perpendicular to the LV long-axis, was calculated separately for each apical imaging plane (A4C, A3C, and A2C) as the average of the integrated longitudinal myocardial velocity curves from the two opposite apical segments (assumed to represent the up and down motion of the 'cap rim'). For this, one motion trace (by definition the 'right-sided' in the image) was inverted (*Figure 1A*). ATM was measured during isovolumic contraction (ATM_{IVC}) and ejection time (ATM_{ET}) as well as for the total cardiac cycle (ATM_{TOT}). The true apex motion perpendicular to the LV long-axis (ATM_{loop}) was reconstructed from the in-plane ATM curves of the three apical views assuming them to intersect at 60° angles (*Figure 1B*) and the main direction and amplitude of the ATM_{loop} was measured.

Conventional indices of dyssynchrony

Conventional tissue Doppler-based dyssynchrony indices were determined according to original publications. We calculated the standard deviation (SD) of time to peak velocity in 12 mid and basal segments (Ts SD12),[15] the difference of time to peak velocity between anteroseptal and posterior wall (Ts AsP),[17] the difference of time to peak velocity between septal and lateral wall (Ts SL)[18] as well as the maximal difference of time to peak velocity in 6 basal segments (Ts Diff6).[19] Cut-off values were applied as published. Conventional dyssynchrony assessment was performed by one observer, blinded to any clinical and haemodynamical data. Moving image loops were not reviewed during this analysis in order to avoid any bias.

Visual assessment of apex motion

Apical rocking was visually assessed by four readers: two cardiologists with 3 (reader 1) and 10 (reader 2) years and two sonographers with 1 (reader 3) and 16 (reader 4) years of echo experience. The sonographers were trained in apical rocking assessment with 10 example data sets which were not part of the study. All readers had only access to the grey scale image loops of the three apical image planes and were unaware of any patient data except the information on ischaemic or non-ischaemic origin of the heart failure. Response to CRT should be assumed, if a short-lived early septal motion of the apex and a predominantly lateral motion during ejection were seen. Any other time course of apical rocking should be regarded as non-predictive. In addition, readers were encouraged to consider all other information disclosed in the echo loops (global and regional function, scar extent, etc.).

Statistical analysis

Grouped data are presented as mean and SD or as median and interquartile range, as appropriate. Comparisons between groups were done by means of a *t*-test or Mann–Whitney *U* test. For multiple groups, comparisons were made using analysis of variance or a Kruskal–Wallis test, with *post hoc* pairwise comparisons between the groups whereby adjustments to the significance level were made using the Tukey–Kramer method or Dunn's multiple comparison test, respectively. For the comparison of paired samples, a paired-test or Wilcoxon signed-rank test was used. Receiver operating characteristics (ROC) curves and their area under the curve were calculated to assess the discriminative power of parameters. Area under the curve (AUC) values were compared using the method offered by MedCalc. Categorical variables were compared using χ^2 test with Yates correction. Data sets from 27 patients in changed order were re-analysed by one reader after 3 months. Kappa statistics were

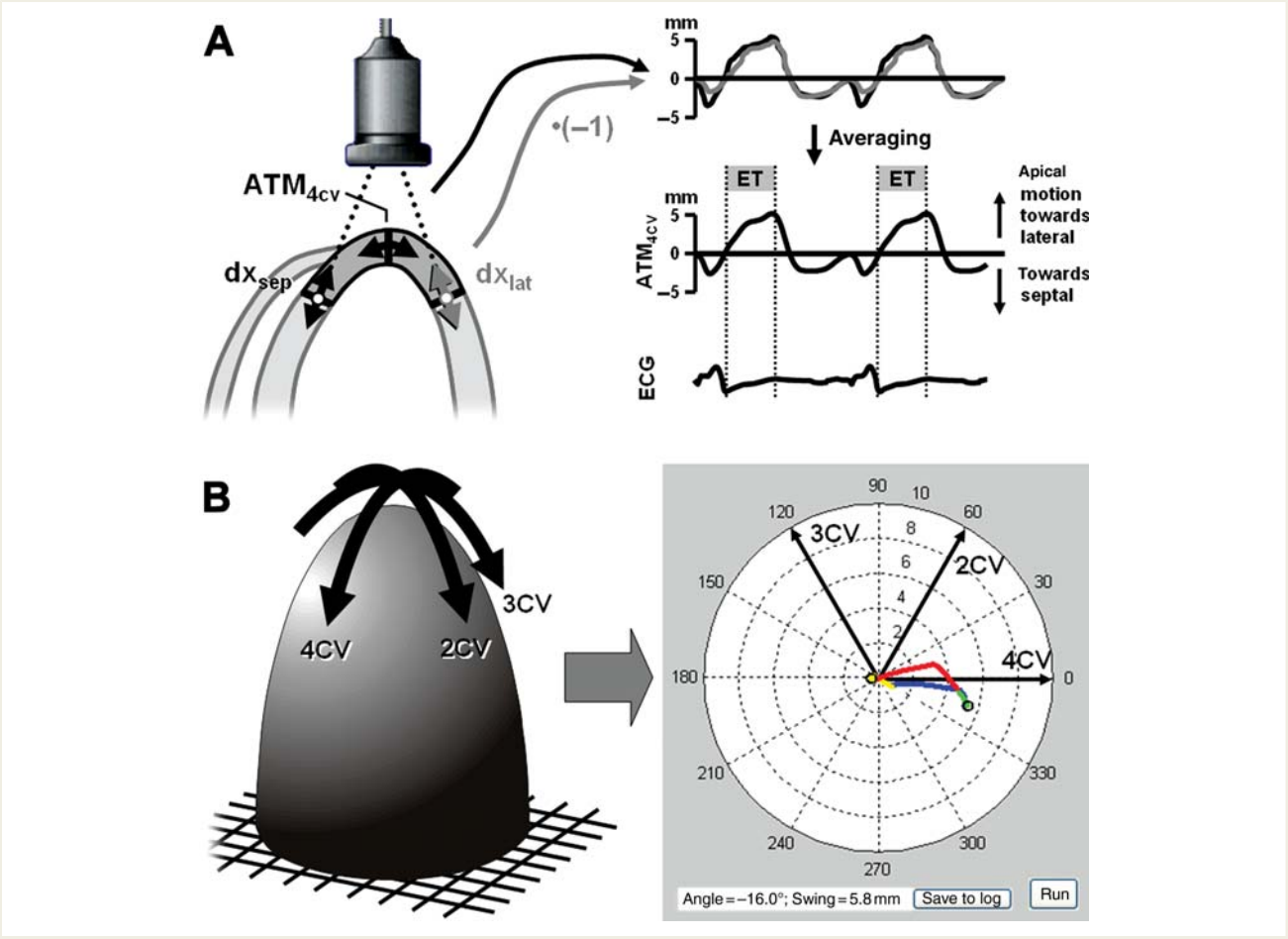

Figure 1 (*A*) Calculation of the apical transverse motion (ATM) curve exemplified for the apical 4-chamber view. Assuming that the transverse apex motion in the apical 4-chamber view (ATM_{4CV}) is the average of the longitudinal apical septal (dx_{sep}) and the inverted lateral motion (dx_{lat}), longitudinal velocity traces are obtained from both apical segments by tissue Doppler (left). Velocity traces are integrated to motion traces. After inverting the right-sided trace (grey), traces are averaged to obtain the ATM-curve in the plane of the apical 4-chamber view (right). The example shows a typical left bundle branch block pattern with early short septal motion of the apex and lateral motion during ejection time (ET). ECG, electrocardiogram. (*B*) Calculation of the apex motion loop. Left: Combing the in-plane ATM traces from all three apical image planes allows reconstructing the true motion of the apex. Right: Screenshot of a ATM loop reconstruction in a patient with left bundle branch block. The polar plot shows the reconstructed transverse displacement of the apex during a cardiac cycle (viewing position: from apex towards base). Black arrows indicate the assumed orientation of three scan planes (2CV, 3CV, 4CV, apical 2-, 3-, and 4-chamber view). Time intervals are colour coded (yellow, isovolumic contraction; red, ejection time; green, isovolumic relaxation; blue, diastole). Black circles indicate the largest extension of the loop and the main direction of motion.

applied to determine the intra-observer variability. All statistical tests were two-sided and assessed at the 5% significance level. We used the programs InStat 3 and Prism 4 (GraphPad Software Inc., La Jolla, USA) and MedCalc (MedCalc Software, Mariakerke, Belgium) for statistical calculations.

Results

Patient population, cardiac resynchronization therapy response

Characteristics of our patient population are summarized in *Table 1*.

Forty patients (58%) responded to CRT. Responders and non-responders did not differ in clinical and conventional echocardiographic baseline parameters. During follow-up, LVEF improved significantly in responders (25 ± 6 vs. $37 \pm 9\%$, $P < 0.0001$) but not in non-responders (28 ± 8 vs. $29 \pm 7\%$; $P = 0.904$). Likewise, ESV decreased in responders, but not in non-responders (-34 ± 17 vs. $+4 \pm 24\%$, $P < 0.001$).

Apical transverse motion

Calculation of ATM was possible in 67 patients (97% feasibility). The additional time demand on top of regular segmental colour tissue Doppler analysis was in the range of seconds. ATM did not correlate significantly with baseline LVEF or QRS duration.

The maximum amplitude of the reconstructed ATM_{loop} differed significantly between responders and non-responders (3.3 ± 1.6 vs. 1.9 ± 1.4 mm; $P = 0.002$). With a cut-off value of 2.8 mm,

Table 1 Baseline characteristics

	Responder	Non-responder	*P*-value
Clinical			
Age	62.6 ± 10.8	64.2 ± 8.7	0.508
NYHA class	3.05 ± 0.48	3.09 ± 0.42.	0.757
QRS duration (ms)	169.9 ± 20.2	163.1 ± 27.7	0.252
Ischaemic aetiology ($n = 36$)	15 (41.7%)	21 (58.3%)	0.405
Non-ischaemic aetiology ($n = 33$)	25 (75.8%)	8 (24.2%)	0.005
Haemodynamics			
LV ejection fraction (%)	25.3 ± 6.	28.4 ± 7.7	0.058
LV end-systolic volume (mL)	193.9 ± 68.5	181.5 ± 67.9	0.464
LV end-diastolic volume (mL)	249.4 ± 90.1	248.8 ± 75.2	0.975
LV end-systolic diameter (mm)	62.8 ± 10.4	61.65 ± 10	0.643
LV end-diastolic diameter (mm)	71.7 ± 9.7	71 ± 8	0.967

this parameter would have predicted reverse remodelling with a sensitivity, specificity, and accuracy of 70, 90, and 76% (*Figure 2A*). ROC analysis revealed an area under the curve of 0.82 (CI 0.71–0.93).

In-plane ATM differed between the three imaging planes and the time intervals considered (*Tables 2* and *3*). ROC analysis revealed that ATM in the four-chamber view plane during ejection time (ATM_{A4C_ET}) would have been the best predictor of CRT response (AUC 0.89, CI 0.78–0.97; *Figure 3* and *Table 3*). A cut-off of 1.5 mm distinguished between responders and non-responders with a sensitivity, specificity, and accuracy of 75, 96, and 83%, respectively (*Figure 2A*). ATM_{ET} and ATM_{TOT} differed in the measured values, but not in their predictive value for CRT response. ATM_{IVC} was not predictive (*Table 3*): although ATM_{ET} towards the lateral wall was found in 95% of responders (χ^2 $P = 0.0003$ vs. non-responders), ATM_{IVC} towards the septum was recognized in only 65% of responders (χ^2 $P = 0.735$ vs. non-responders).

Reproducibility of apical rocking estimates in our lab has been published earlier and is $<0.2 \pm 0.6$ mm.[9]

Visual interpretation of apical rocking

Visual assessment of apical rocking resulted in an average sensitivity, specificity, and accuracy for prediction of CRT response of 89, 75, and 83%, respectively (*Figure 2A*). Reading accuracy from all four readers ranged from 77 to 87% (*Figure 4*). We found no relation between reading results and the reader's experience.

The repeated reading of a subset of cases showed a low intra-observer variability ($\kappa = 0.85$).

Comparison to conventional dyssynchrony parameters

The accuracy of conventional dyssynchrony parameters ranged from 48 to 56% and was significantly lower than for quantitative (76–83%) and visual assessment (83%) of apical rocking ($P < 0.001$, *Figure 2A*). The AUC of the conventional parameters was in the range of 0.48–0.63 (CI 0.33–0.77) and with this significantly lower than for ATM_{A4C_ET} (0.89, CI 0.78–0.97, $P \leq 0.003$ vs. all of the above).

The added predictive value of the different approaches of dyssynchrony assessment is presented in (*Figure 2B*).

Discussion

Apical rocking is a frequent echocardiographic finding in patients with dilated cardiomyopathy.[20,21] We have recently suggested a method to quantify apical rocking by measuring the transverse motion of the LV apex and could show that this motion is an integrative marker of both temporal and regional inhomogeneities of LV function.[9] The results of the current study demonstrate that the quantitative and visual assessment of apical rocking is clinically feasible, reproducible and that it has a predictive value for reverse remodelling during CRT.

Apical rocking results from an imbalance of myocardial function due to intraventricular conduction delays, regional damage, or both.[9,22–24] In CRT responders, we noted a typical early septal contraction which pulls the apex towards the septum. This finding is in concordance with other studies proving an early septal contraction by means of demonstrating a short-lived bounce in the septum ('septal flash').[10,25]

We interpret ATM_{IVC} and septal flash as being induced by the same early septal contraction. Detecting such a short-lived event by measuring the minor early ATM towards the septum (ATM_{IVC}), however, is challenging and was therefore found to have a limited predictive value for CRT response. In contrast, the long-lived lateral motion of the apex during ejection time wall is easier to detect which explains the better performance of ATM_{ET}. We therefore suggest to consider a lateral motion of the apex during ET as predictive for response to CRT. Besides that, published reports on septal flash mention its limited value at rest.[10]

Previously suggested parameters for dyssynchrony assessment are mainly based on the timing of myocardial velocity peaks.[6] Those are not directly related to regional myocardial function and therefore may in part reflect temporal inhomogeneities but cannot detect differences in regional myocardial function.[7]

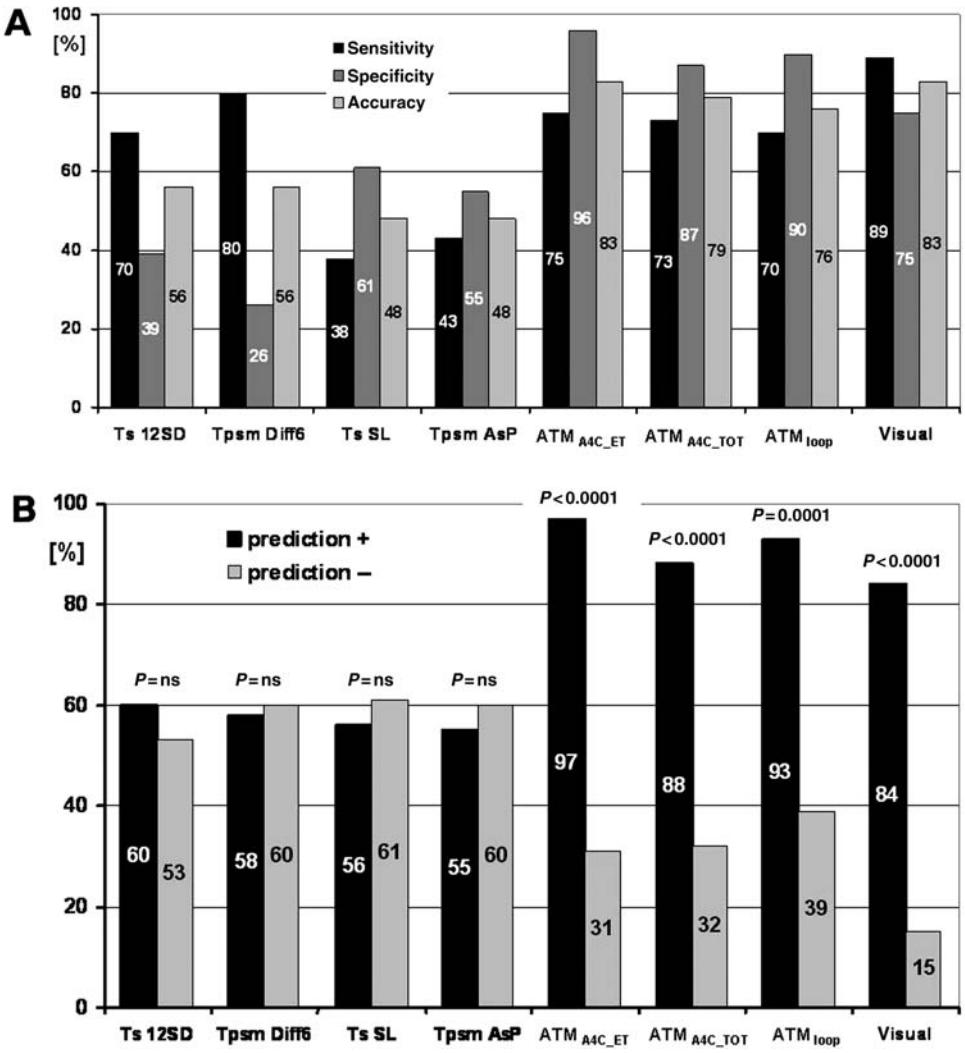

Figure 2 (*A*) Comparison of sensitivity, specificity, and accuracy of conventional dyssynchrony parameters and quantitative and visual apical transverse motion estimation. Ts, time to peak positive systolic myocardial velocity; Tpsm, time to highest peak positive velocity (including post-systolic motion); Ts SD12, standard deviation of time to peak velocity in 12 mid and basal segments; Tpsm Diff6, maximal difference of time to peak velocity in 6 basal segments; Ts SL, the difference of time to peak velocity between septal and lateral wall; Tpsm AsP, the difference of time to peak velocity between anteroseptal and posterior wall; ATM_{A4C_ET}, apical transverse motion in the apical 4-chamber view during ejection time; ATM_{A4C_TOT}, the same during the entire cardiac cycle; ATM_{loop}, maximum extent of the apical transverse motion loop, as reconstructed from all three apical views; Visual—visual assessment (mean of four readers). (*B*) Added predictive value of different predictors of cardiac resynchronization therapy response. Bars indicate the percentage of responders when the respective parameter predicted response (black) or not (gray).

However, site and extent of dysfunctional myocardium influences CRT success.[4,5,26,27] Accordingly, peak-velocity-based parameters were shown to be of only limited value in predicting CRT response in our study. Our findings show a performance of conventional parameters of dyssynchrony which is worse than reported in the initial publications about the respective parameters. However, they are in full concordance with more recent, larger scale trials which also found a limited robustness and predictive value of these parameters.[8,10,16,28,29,30,31]

The quantitative analysis of apical rocking showed a higher accuracy than conventional parameters for the prediction of CRT response. This was in part due to the better sensitivity of ATM, but also due to its always higher specificity.

Our results suggest that compared with quantifying, visual assessment of apical rocking yields a comparable accuracy in predicting CRT response. This is in concordance with other studies reporting similar results in quantitative and visual dyssynchrony assessment.[21] Although the short septal motion of the apex is sometimes difficult to recognize, particularly at low frame rates,[32] the long-lasting apex motion towards the lateral wall during ejection time can be easily seen. For an experienced echocardiographer, a short training period appears sufficient. We therefore suggest to always consider

the visual evaluation as valuable part of the echocardiographic assessment of LV dyssynchrony.

Limitations

Similar to other CRT studies, our definition of response was solely based on the clear evidence of reverse remodelling.[15,33] Less strict definitions, e.g. minor EF changes or improvement of NYHA class, however, would have weakened the message of this study.

As in all CRT studies, we have no proof that the non-response to therapy is solely due to insufficient patient selection. Suboptimal lead placement or unfavourable pacemaker settings must also be considered. However, care was taken to minimize this risk by coronary venogram-guided lead placement and echo-guided pacemaker optimization after device implantation.

All patients met current guideline criteria for CRT treatment. Further studies are needed to investigate the predictive value of apical rocking in patients with better EF, narrower QRS, and better clinical states.

As in clinical routine, our study group comprised patients with cardiomyopathy of ischaemic and non-ischaemic origin. Although we could supply evidence in favour of our proposed new method on a group level, our study was not powered to further investigate the influence of infarct size and location on apical rocking in detail which requires further investigation.

Patients were only studied at rest. Recent publications suggested, however, that a stress test might support the prediction of CRT

Table 2 Apical transverse motion

	Responders (mean ± SD)	Non-responders (mean ± SD)	*P*-value
ATM_{ET} (mm)			
A4C	2.17 ± 1.53	0.06 ± 1.99	<0.0001
A2C	1.16 ± 1.43	0.54 ± 0.98	0.072
A3C	−1.24 ± 1.65	0.17 ± 0.97	0.0009
ATM_{TOT} (mm)			
A4C	3.26 ± 1.66	1.56 ± 0.86	<0.0001
A2C	2.01 ± 1.29	1.40 ± 0.81	0.0473
A3C	2.39 ± 1.57	1.30 ± 0.71	0.0051

ATM_{ET}, apical transverse motion during ejection time; ATM_{TOT}, apical transverse motion during entire cardiac cycle; A4C, A3C, A2C, apical 4-, 3-, and 2-chamber view; SD, standard deviation.

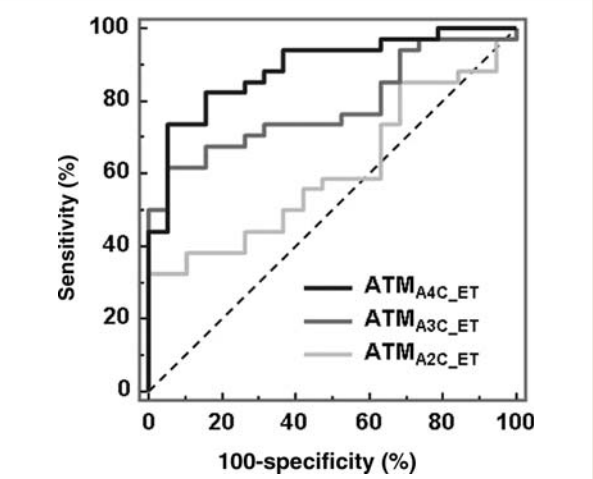

Figure 3 Receiver operating characteristic analysis of apical transverse motion during ejection time for prediction of cardiac resynchronization therapy response. Comparison of apical transverse motion from the three apical planes. Amplitude of apical transverse motion in apical 4-chamber view would have been the best predictor of reverse remodelling. Refer to *Table 3* for area under the curve values. ATM_{A4C_ET}, ATM_{A3C_ET}, ATM_{A2C_ET}, apical transverse motion during ejection time in the apical 4-, 3-, and 2-chamber view, respectively.

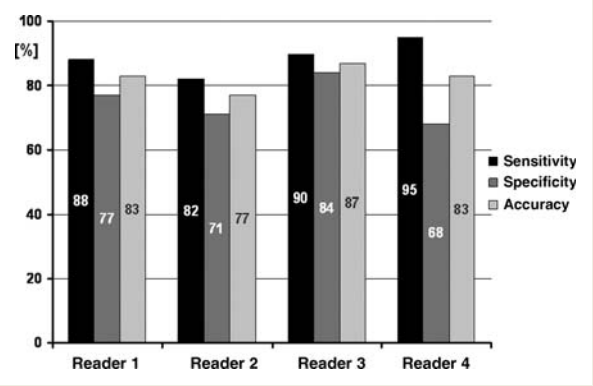

Figure 4 Sensitivity, specificity, and accuracy of visual assessment for prediction of cardiac resynchronization therapy response—detailed results from all readers.

Table 3 Apical transverse motion: receiver operating characteristics analysis

	ATM_{IVC}		ATM_{ET}		ATM_{TOT}	
	AUC	95% CI	AUC	95% CI	AUC	95% CI
A4C	0.53	0.39–0.65	0.89	0.78–0.96	0.83	0.71–0.91
A3C	0.59	0.45–0.72	0.77	0.64–0.88	0.721	0.58–0.83
A2C	0.53	0.40–0.66	0.63	0.50–0.75	0.64	0.50–0.76

ATM_{IVC}, apical transverse motion during isovolumic contraction; ATM_{ET}, apical transverse motion during ejection time; ATM_{TOT}, apical transverse motion during entire cardiac cycle; A4C, A3C, A2C, apical 2-, 3-, and 4-chamber view; AUC, area under receiver operating characteristic curve; CI, confidence interval.

response.[25,34] It remains the task of future studies to investigate the phenomenon of apical rocking under stress conditions and to determine a possible added predictive value of such an approach.

Clinical perspective and conclusion

Our study objectifies the often unexpressed assumption, that mechanical dyssynchrony is required for successful resynchronization, and that the trained human eye is indeed able to detect such dyssynchrony.

Apical rocking is a new marker, integrating both functional and temporal inhomogeneities within the LV myocardium. Its quantitative assessment is feasible in the clinical setting of CRT candidate selection and has advantages over peak-velocity-based parameters. With a trained eye, even its visual estimation may be sufficient.

We therefore suggest to use quantitative or qualitative measures of apical rocking for the prediction of CRT response.

Conflict of interest: none declared.

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