Relation between left ventricular wall dimensions in cardiac resynchronization therapy candidates and echocardiographic and clinical outcome

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Abstract

Background: Left ventricular (LV) wall and cavity dimensions in cardiac resynchronization therapy (CRT) candidates may be important to determine the efficacy of CRT pacing. Several studies have indicated that in left bundle branch block (LBBB) the late-activated LV free wall is thick and the interventricular septum is thin, but none of them related these LV dimensions to outcome.

The objective was to determine the thickness of the LV wall, both at the septum and at the free wall. The relation between this thickness and the outcome of CRT was investigated.

Material and methods: Wall thicknesses in the PROSPECT cohort were analyzed by echocardiographic measurements and related to the outcome of these patients. Outcome was measured in two ways: LVESV reduction of ≥15% and a clinical composite score.

Results: The LV posterior wall was significantly thinner than the interventricular septum (1.07 vs. 1.12 cm, $p<0.0001$). Although posterior wall thickness (PWT) and septal wall thickness (SWT) were not predictors of CRT outcome, the SWT/PWT ratio was a significant predictor of outcome as measured by the clinical composite score ($p=0.042$; odds ratio = 0.32). In the case of a high SWT/PWT, less improvement was observed.

Conclusion: The current consensus that in LBBB the free wall is thick and the septum is thin should be reconsidered. The SWT/PWT ratio was predictive of CRT response.

Clinical trial registration information: URL: http://www.clinicaltrails.gov. Unique identifier: NCT00253357.

Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for patients suffering from chronic heart failure, with a left ventricular ejection fraction (LVEF) of ≤35% and a prolonged QRS duration.1 CRT reduces mortality and frequency of hospitalization, and improves functional outcomes in these patients.2 However, the continued existence of non-responders to CRT remains an obstacle. Reported CRT responder rates vary greatly: depending on the outcome measure, they vary from about 15 to 45%.3 Several methods to increase the responder rate such as more adequate patient selection, multipoint pacing and pacing from the inside of the left ventricle (LV) are being investigated.4-6 Current human data on the wall thickness in CRT candidates are very limited. The current (pre)clinical data show that left bundle branch block (LBBB) – present in the majority of CRT candidates – exhibits asymmetric hypertrophy with thicker free walls and thinner septa.7-10 The reason for this is that the free wall is activated late, and therefore has to contribute more to the ejection while the septum is unloaded. This would result in reactive hypertrophy due to the increased workload.7-10 The effect of wall thickness on CRT outcome has, to the knowledge of the authors, not been investigated before. The purpose of our analysis was to shed light on the mechanisms of CRT response and of myocardial changes in dilating hearts, rather than focusing on the clinical applicability.

Methods

This analysis was conducted on the cohort from the Predictors of Response to CRT (PROSPECT) trial. The protocol has been described extensively in the published study design.11 We investigated both of the trial's primary measures of response: left ventricular end systolic volume (LVESV) reduction of 15% or more, and Packer's clinical composite score (CCS). This CCS classifies each patient as either improved, unchanged or worsened based on hospitalization for worsening heart failure, mortality, change in NYHA class and a patient global assessment score.12

Echocardiographic methods

The echocardiographic methods used in the PROSPECT trial were previously reported.13 In short, all participating centers were trained on a pre-specified echocardiographic protocol, and accreditation performed by the core lab was required prior to starting enrolment. Apical 2- and 4-chamber sequences were obtained for volumetric assessment. Wall thickness was obtained from parasternal long axis views. All echocardiographic data were analyzed centrally by a core lab according to a pre-specified echocardiographic measurement manual.

Statistical methods

Continuous variables are noted as mean ± SD. Statistical analysis of differences between free wall thickness and thickness of the interventricular septum at baseline was done by a paired t-test. One-way ANOVA was used to determine the associations between continuous variables (septal thickness, posterior wall thickness or ratio) and LBBB or myocardial infarction (MI). Ordinal logistic regression was used for the influence of continuous variables on outcome measure CCS. Binary logistic regression was used for the influence of continuous variables (septal thickness, posterior wall thickness and their ratio) on outcome measure LVESV reduction >15%. Multivariable linear and logistic regression was used to determine the effect of multiple parameters on an outcome measure.

The data were processed in Microsoft Excel 2010. Statistical analysis was conducted with Minitab software (version 17.3, Minitab Inc., State College, PA, USA). All statistical tests were 2-sided. In all tests a p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

The 426 patients who were included in the PROSPECT study encompassed the full study group. Baseline characteristics are presented in Table 1, and for a detailed description the original publication can be consulted.13 It should be noted that not all investigated parameters were fully documented for all 426 patients, so the analysis often contained a smaller sample size.

Table 1. Baseline characteristics of the PROSPECT cohort

Baseline characteristics	
N	426
Age (years)	67.8 ± 11.0
Gender (% male)	71
NYHA class III (%)	96
QRS interval (ms)	163 ± 22
Ischemia (%)	54
Previous MI (%)	48
LVEF (%)	23.6 ± 7.0
LVEDV (ml)	230 ± 99
LVESV (ml)	168 ± 89

LV pre-implant characteristics

The average posterior wall thickness (PWT) before CRT implant was 1.07 cm ± 0.17 (n=307), which is significantly thinner than the average thickness of the interventricular septum (septal wall thickness, SWT), which was 1.12 cm ± 0.25 (n=306), p<0.0001. The ratio of the thickness of the interventricular septum to the thickness of the posterior wall (SWT/PWT) was 1.05 ± 0.21 (n=305). The end-diastolic diameter (EDD) of the LV before implantation was 6.43 cm ± 1.07 (n=308).

Left-bundle branch etiology and its influence on LV dimensions

The large majority of the PROSPECT cohort had LBBB (86%). When comparing the subjects with and without LBBB etiology, no significant difference was found in PWT (LBBB 1.08 cm ± 0.16, non-LBBB 1.03 ± 0.22 cm, p=0.063) or SWT (LBBB 1.11 cm ± 0.24, non-LBBB 1.13 cm ± 0.29, p=0.581). A significant difference was found in the SWT/PWT wall ratio, where LBBB subjects had an average ratio of 1.04 ± 0.18 while non-LBBB subjects had an average ratio of 1.13 ± 0.30 (p=0.004).

Myocardial infarction and its influence on LV dimensions

A history of MI, independent of its location and without confirmation of a scar, was present in 48% of subjects in the PROSPECT cohort. The MI group did not show a statistically significant difference in SWT compared to non-MI (MI 1.15 cm ± 0.25, non-MI 1.09 cm ± 0.24, p=0.060) but it could be noted that the septa in the MI group were 0.06 mm thicker. There was also no significant difference in PWT between MI and non-MI groups (MI 1.06 cm ± 0.17, non-MI 1.09 cm ± 0.17, p=0.113). A significant difference was found in the SWT/PWT wall ratio: subjects with a history of MI had a higher ratio compared to subjects without a history of MI (MI 1.09 ± 0.20, non-MI 1.01 ± 0.21, p=0.001).

LV dimensions and outcome

LV dimensions were investigated for associations with both of the outcome measures (CCS and successful LVESV reduction of >15%). No significant association was found between the LV dimensions PWT or SWT and either of the outcome measures. However, an ordinal logistic regression showed that the SWT/PWT ratio was a significant predictor for CCS (p=0.042). When dividing the cohort into quintiles based on their SWT/PWT ratio, it could be seen that the quintile with the lowest ratio had a 75.4% improvement rate. This steadily declined with every higher quintile, and the quintile with the highest ratios had an improvement rate of 60.7%. The difference between improvement in the lowest and highest ratio quintile was a decrease of 14.7%. The worsened category remained constant up until the fifth quintile, while the unchanged category increased (see Figure 1). There was no significant association between PWT, SWT or SWT/PWT ratio and the outcome measure LVESV reduction of >15%.

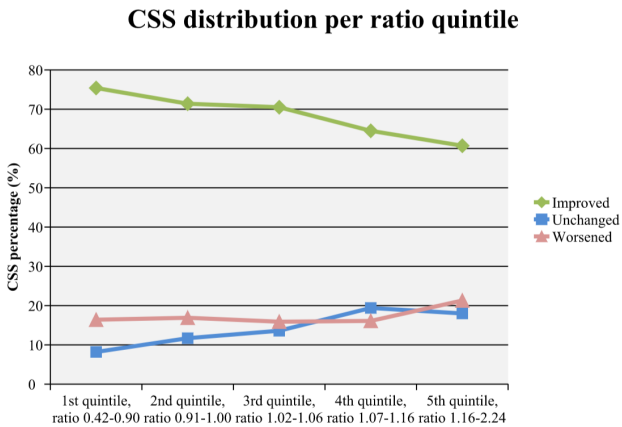

Figure 1. SWT/PWT was split into quintiles and CCS distribution was plotted for each quintile. The improvement percentage steadily declines with an increase in SWT/PWT ratio. The absolute difference in improvement percentage between the lowest and highest quintile is a decrease of 15%.

LV dimensions and outcome: influence of MI

Both SWT/PWT ratio and MI history were univariate predictors of CCS. Ordinal logistic regression for SWT/PWT ratio as predictor of CCS has a p-value of 0.042, while an independent regression for MI as a predictor for CCS has a p-value of 0.035. When combining these two factors into a multivariable logistic regression model, the p-value for SWT/PWT ratio is 0.051, while the p-value for MI is 0.806. This suggests that SWT/PWT is the more important factor of the two for the determination of CCS. To gain further insight into this, the cohort was divided into four groups based on whether they had a history of MI, and whether they had a high or low ratio (an average SWT/PWT ratio >1.05 was considered high). It was found that both groups with a low ratio had an improvement rate of 72%, independent of whether they had a history of MI or not. The groups with large SWT/PWT ratios did worse, with an improvement percentage of 62% for the MI group with large ratios, and an improvement percentage of 67% for the non-MI group with large ratios (see Figure 2). The p-value for the interaction with SWT/PWT ratio when added to the model was p=0.98.

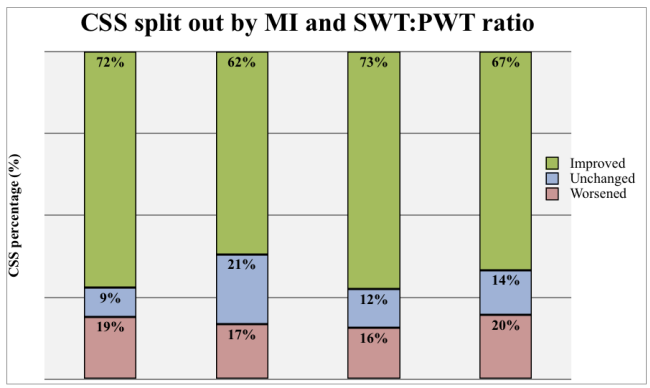

Figure 2. The cohort was divided into four groups based on whether the subject had a history of MI, and whether their SWT/PWT ratio was above or below average. The percentage of improved, unchanged and worsened CCS for these groups is presented. The groups with a low SWT/PWT ratio have the largest improvement percentages, irrespective of MI history.

Discussion

In the PROSPECT cohort, the average PWT was 1.07 cm ± 0.17, the SWT was 1.12 cm ± 0.25, and the left ventricular end-diastolic diameter (LVEDD) before implantation was 6.43 cm ± 1.07. In adults without cardiovascular disease, a cardiovascular MRI study found that the PWT of males was 0.99 cm, with an SWT of 1.01 cm and an LVEDD of 5.02 cm.14 Compared to this healthy population, the subjects of the PROSPECT cohort have hypertrophied, dilated hearts.

It is surprising that the average thickness of the interventricular septum of these CRT candidates was significantly thicker than the average thickness of the posterior wall. This is reflected by the finding that the SWT/PWT ratio is 1.05 on average. This is the opposite of previous findings that led to the consensus that subjects with LBBB have asymmetric hy-

pertrophy with thick free walls and thin septa.7-10 However, another study that investigated the effect of CRT on LV mass and wall thickness had similar findings as our cohort: they also found that CRT-D patients had thicker septa than posterior walls at baseline (SWT 0.83 cm ± 0.69, PWT 0.81 cm ± 0.66).15

We propose three explanations for the discrepancy between our findings and the consensus of asymmetric hypertrophy with thicker free walls and thinner septa. First, the hearts in the PROSPECT cohort were dilated. With regression analysis we found that an increase in LVEDD leads to a decrease in both SWT and PWT ($p<0.001$). If this dilatation would affect the free wall more than the septum, this could explain our finding that the septum is thicker than the posterior wall. Reasons why the free wall might be more sensitive to thinning because of dilatation might involve mechanical changes due to long term late activation or differences in fiber direction in the free wall compared to the septum. Secondly, about half of the PROSPECT subjects had a history of MI. It is known that wall thinning takes place after MI, while non-infarcted regions can show a compensatory increase in contraction force and wall thickening.16,17 It could be argued that if the blood supply is impaired in these post-MI PROSPECT subjects and fibrotic scarring is present, occurrence of the expected hypertrophy might be hindered. This could explain the difference in SWT/PWT ratio between MI and non-MI subjects, where MI subjects had significantly higher SWT/PWT ratios than non-MI subjects. Thirdly, the stage of disease might play a role. The subjects from the PROSPECT cohort had NYHA class III-IV heart failure. It is possible that they once had asymmetric hypertrophy, as found in other studies, but it was lost over the course of their disease. This would explain why the pre-CRT implant measurements no longer reflect the expected asymmetric hypertrophy. These three hypotheses as an explanation for our finding that the free wall is thinner than the septum in CRT candidates should be investigated further.

The PWT and SWT were not significant predictors of CRT outcome. However, SWT/PWT ratio was a significant predictor of CRT outcome measured by the clinical composite score ($p=0.042$). If the SWT/PWT ratio increases, the chance of improvement decreases. Possible reasons why this could be the case could be intertwined with the previous hypotheses. It was shown that subjects who had a history of MI had significantly larger ratios. It is also known that subjects with ischemic cardiomyopathy have a lesser response to CRT compared to nonischemic patients.18,19 This raised the question whether it was the underlying MI (which subsequently caused a higher ratio) that was the reason for a decrease in improvement in CCS, rather than the ratio itself. However, multivariate regression showed that it is the SWT/PWT ratio that is the more important factor of the two. We found that the improvement percentage is identical for MI and non-MI subjects, as long as their SWT/PWT ratio is low. This makes underlying MI as a reason why high ratios have poorer outcomes less plausible. Another possible explanation why a high SWT/PWT ratio negatively affects the response to CRT is the stage of disease. As previously discussed, a further advanced stage of heart failure might underlie the thicker septa and thinner free walls. It has also been shown that non-responders to CRT have a more advanced stage of the disease.20 Therefore, if progression of heart failure causes the SWT/PWT ratio to increase, and if progressed heart failure has more non-responders, there is a connection between ratio and outcome. The previously mentioned mechanisms by which a high SWT/PWT negatively affects the response to CRT are all indirect effects, but it is also possible that SWT/PWT ratio directly affects the response to CRT. An example of this is a more favorable environment for CRT; if a thinner septum and thicker free wall somehow create more favorable pacing conditions, this could explain why SWT/PWT is a significant predictor of outcome.

Limitations

All wall measurements were obtained at end-diastole. During the pre-ejection phase, the septum in LBBB patients actively contracts, which leads to thickening, while the lateral wall stretches and thins.21 If our measurements were taken during this septal contraction, our findings with thick septa and thin free walls might simply reflect this phenomenon. However, since the measurement guidelines defined the onset of systole as the beginning of Q, this seems highly unlikely.

A limitation of the subsection regarding the influence of MI was the fact that the history of MI was retrieved from the patients' medical history, was analyzed regardless of location, and presence of a scar was not confirmed. Presence of a scar as an explanation for the lack of asymmetric hypertrophy in the free wall warrants further research, since it was shown that subjects with MI have smaller SWT/PWT ratios, preferably with identification of the location of this scar.

A statistical limitation was that although SWT/PWT ratio was a significant predictor of CCS, the p-value of this analysis was only slightly under the significance threshold of $p=0.05$ ($p=0.042$). Furthermore, SWT/PWT was not a significant predictor for the other outcome measure, an LVESV reduction of >15%. This is not surprising, since earlier research has shown that the agreement between these two outcome measures is poor ($r=0.13$).22 Hence, caution is required when drawing the conclusion that SWT/PWT is a predictor of the outcome of CRT, and further research is warranted. Furthermore, no confirmed relationship of this ratio or wall thickness to LVESV reduction was observed.

Clinical perspective

The current belief that in LBBB etiology the septum is thin and the free wall is thick should be reconsidered. PWT and SWT were not significant predictors of CRT outcome. The SWT/PWT ratio was found to be a significant predictor of CRT response when the outcome was measured with Packer's Clinical Composite Score. The difference between the lowest ratio quintile (75% response) and the highest ratio quintile (60% response) was striking and could be of clinical relevance. The predictive capacity of this parameter should be evaluated in other cohorts and its potential for use as a clinical predictor of CRT response should be carefully assessed.

Conclusions

Controversy exists about the regional left ventricular wall thickness and its change during CRT in dyssynchronous patients. Our findings may add justification for lead navigation approaches to optimal myocardial targets in CRT based on local wall thickness. However, no cause and effect was demonstrated and the study did not assess the optimal pacing target. Regional wall thickness can easily be measured using modalities already available and part of the care pathway (ECHO or MRI). Novel lead designs (such as quadripolar leads) can be used to adjust stimulation electrodes and subsequent efficacy of CRT both before and throughout CRT application.

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Disclosures:

TB, BS, BG and RC were employees of Medtronic plc at the time of study execution.

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