Evaluation of global left ventricular function and mechanical dyssynchrony in patients with an asymptomatic left bundle branch block: a real-time 3D echocardiography study

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Background A left bundle branch block (LBBB) affects both global left ventricular (LV) function and mechanical dyssynchrony. The aim was to evaluate global LV function and mechanical dyssynchrony with real-time 3D echocardiography (RT3DE), in asymptomatic LBBB patients, healthy volunteers and patients with symptomatic heart failure (HF) and a LBBB. Furthermore, the relation between presence or absence of symptoms of HF and mechanical dyssynchrony was investigated.

Methods RT3DE was performed in 61 consecutive patients: 16 healthy volunteers, 22 patients with an asymptomatic LBBB and 23 patients with symptomatic HF and a LBBB. Global LV function and the systolic dyssynchrony index (SDI) were measured.

Results In healthy volunteers, mean LV ejection fraction was 54 ± 5%, in asymptomatic LBBB patients 50 ± 9%, and in HF patients 29 ± 9%. SDI was 5.6 ± 3.6%, 7.3 ± 3.2% and 12.8 ± 4.8% for healthy volunteers, asymptomatic LBBB patients and HF patients respectively. SDI differed significantly between HF patients and both other groups. A cut-off value for SDI for presence of symptoms of HF was 10.8%.

Conclusion Asymptomatic LBBB patients have more depressed global LV function than healthy volunteers have; patients with symptoms of HF and a LBBB have severe global LV dysfunction. Asymptomatic LBBB patients have an intermediate mechanical dyssynchrony; HF patients with a LBBB have the most severe mechanical dyssynchrony. A substantial amount of mechanical dyssynchrony might be accompanied by the presence of symptoms of HF.

KEYWORDS
3D echocardiography;
Left bundle branch block;
Heart failure;
Healthy volunteers

Introduction

In an animal model, left ventricular (LV) mechanical dyssynchrony is observed immediately after artificial induction of a left bundle branch block (LBBB). Persistent mechanical dyssynchrony contributes to progressive ventricular remodeling and impaired systolic LV function.1 Mechanical dyssynchrony may partially be responsible for the increased morbidity and mortality in heart failure (HF) patients with conduction abnormalities as a LBBB, compared to HF patients without a LBBB.2–5

In addition, in patients without underlying structural cardiac disease, except the presence of a LBBB, subtle impaired systolic and diastolic LV functions are frequently found.5 However, impaired function in these patients is not always recognized because of lack of clinical symptoms.6–8 Currently, the most widely used methods for the clinical assessment of LV function and mechanical dyssynchrony are two-dimensional (2D) echocardiography and tissue Doppler imaging.9–11 Transthoracic real-time three-dimensional echocardiography (RT3DE) is a relatively novel imaging technique. It offers the unique opportunity to evaluate global LV function fast and accurate, without presumptions and with comparable results as 2D echocardiography and magnetic resonance imaging.12–15 In addition,
combined with specially designed software, RT3DE provides detailed quantitative information of mechanical dyssynchrony.\textsuperscript{16–18} So far, the relation between mechanical dyssynchrony and presence or absence of symptoms of HF is unknown.

Therefore, we designed a prospective cross-sectional study to assess mechanical dyssynchrony in consecutive LBBB patients, with primary focus on asymptomatic LBBB patients. The first purpose of this study was to evaluate global LV function and the amount of mechanical dyssynchrony with RT3DE in asymptomatic LBBB patients compared to healthy volunteers and patients with symptomatic HF and a LBBB. The second purpose was to evaluate the association between LV mechanical dyssynchrony and the presence or absence of symptoms of HF.

**Methods**

**Study population**

Sixty-three subjects were studied, consisting of seventeen healthy volunteers with no abnormal findings during physical examination, no conduction abnormalities on electrocardiogram; twenty-four consecutive asymptomatic LBBB patients, with no history of structural cardiac disease and no abnormal findings during physical examination, New York Heart Association function class (NYHA) I and twenty-six consecutive symptomatic HF patients with a LBBB, NYHA II–III, without pulmonary hypertension, were screened. A LBBB was diagnosed according to standard electrocardiography criteria: a QRS duration greater than 120 ms, absence of initial septal Q waves, a broadened R wave in the left precordial leads, and an initial R wave followed by a wide, deep S wave in the right precordial leads on a 12-lead electrocardiogram. Symptoms of HF included dyspnoea, ankle oedema, nocturia, fatigue and reduced exercise tolerance.

Asymptomatic LBBB patients were recruited out of the patients that were referred to our cardiology department because of a coincidentally discovered LBBB during screening for minor surgery, insurance screening, etc. Some of the patients did have hypertension, which they were medically treated for, however, standard 2D echocardiography revealed no signs of LV hypertrophy.

Only age-matched patients with sinus rhythm and an adequate echo window during 2D echocardiography were allowed to participate in this study. The local ethical committee approved the study protocol.

**Transthoracic real-time 3D echocardiography**

For RT3DE acquisitions, an echo machine fitted with a $\times$4 matrix-array transducer, with three thousand ultrasound sending and receiving elements (Sonos 7500, Philips Medical Systems, Andover, USA), was used. Transthoracic apical acquisitions were made during 5–7 s breath-hold, with the patient in left lateral position. Care was taken to include the entire LV volume within the pyramid-shaped 3D scan-volume. Due to the sector width of the acquired volume, four alternate heart cycles and a constant RR interval were obligatory to create a full-volume acquisition of the LV. All subjects successfully underwent RT3DE and all RT3DE acquisitions were performed by the same echo technician.

**Analysis of real-time 3D echocardiography**

Specially designed software (Research-Arena 1.2.1\textsuperscript{TM} 4D LV-Analys\textsuperscript{s}©, TomTec Imaging Systems, Munich, Germany) was used for quantification of global ventricular function and regional mechanical dyssynchrony. In apical long-axis planes of the LV, endocardial contours were semi-automatically detected during the complete cardiac cycle. Based on these contours, a LV cast as shown in Figure 1 was created. Using this LV cast, a global time-volume curve during the cardiac cycle was generated and end-systolic volume (ESV), end-diastolic volume (EDV) and ejection fraction (EF) were obtained.

**Quantification of left ventricular mechanical dyssynchrony**

For the evaluation of mechanical dyssynchrony, the LV cast was divided into 16 pyramid-shaped segments; the top pointed toward a non-fixed central point of gravity, whereas the basal parts of the segments were adjacent to the corresponding segments of the LV as described by the American Society of Echocardiography.\textsuperscript{19} For each segment, a regional time-volume curve was obtained. Examples of regional time-volume curves from a healthy volunteer, asymptomatic LBBB patient and a symptomatic HF patient with a LBBB, are shown in Figure 2.

From the regional time-volume curves, the systolic dyssynchrony index (SDI)\textsuperscript{20} was derived. SDI is based on the standard deviation of mean time-to-minimal regional volume of 16 LV segments (six basal, six mid-segments and four apical segments) during a cardiac cycle. In other words, SDI is the dispersion of time-to-minimal regional volume for all 16 LV segments. Time is represented as percentage of the RR interval to allow comparisons of different patients which otherwise could be influenced by RR interval duration.

![Figure 1](image-url) Example of RT3DE evaluation of global LV function and mechanical dyssynchrony. The segments displayed on the bulls eye-plot correspond to the segments of the LV cast. Of each segment, as well as for the whole LV cast, a time-volume curve can be obtained and used for evaluation of global LV function and mechanical dyssynchrony. The grey arrow in the LV cast is a navigation tool.
Statistical analysis

Data are expressed as mean value ± SD. For comparison of means between the three groups, a one-way ANOVA-test combined with a post-hoc Bonferroni analysis was used. Pearson’s correlation coefficient was used for association between continuous variables. A probability value of $P < 0.05$ was considered as statistically significant. Inter-observer and intra-observer agreement were assessed with Bland-Altman method, intra- and interclass correlation coefficient, and with the average difference between readings, corrected for their mean (variability). An intra- and interclass correlation coefficient value $>0.75$ was considered consensus. The optimal cut-off value of SDI for presence of symptoms of HF was determined with receiver-operator characteristic (ROC) analysis. Data were analysed using standard statistical software (SPSS for Windows version 9.0, SPSS Inc., Chicago, USA).

Results

Subjects

Due to poor acoustic window, two asymptomatic LBBB patients (9%) and two symptomatic HF patients with a LBBB (9%) were excluded. A total of 61 consecutive patients were enrolled. The final study population consisted of sixteen healthy volunteers (mean age 58 ± 5 years, QRS duration 91 ± 9 ms), twenty-two patients with an asymptomatic LBBB (mean age 60 ± 10 years, QRS duration 146 ± 15 ms) and twenty-three patients with symptomatic HF and a LBBB (mean age 65 ± 7 years, QRS duration 164 ± 35 ms). Twelve (52%) patients with symptomatic HF and a LBBB had an ischaemic cardiomyopathy. None of the studied patients was having pulmonary hypertension. Furthermore, there were more symptomatic LBBB patients with severe mitral regurgitation (13%) than asymptomatic LBBB patients (5%) and healthy volunteers (0%).

QRS duration between both LBBB groups was not significantly different ($P = 0.052$); QRS duration of both LBBB groups differed significantly from healthy volunteers ($P < 0.0001$ for healthy volunteers vs. asymptomatic LBBB patients and $P < 0.0001$ for healthy volunteers vs. HF and LBBB patients). More patient characteristics are depicted in Table 1.

Global left ventricular function

In Table 2, global LV function parameters of the three groups are shown. Between healthy volunteers and asymptomatic HF patients, no significant difference in EF, ESV and EDV of both groups was observed. RT3DE derived EF, ESV and EDV in healthy volunteers differed significantly from symptomatic LBBB patients ($P < 0.0001$ for all comparisons). Asymptomatic LBBB patients differed significantly from symptomatic LBBB patients according to EF, ESV and EDV ($P < 0.0001$, $P = 0.011$ and $P < 0.0001$ respectively). Figure 3 displays EF of the three groups. As shown in Table 2, asymptomatic LBBB patients and symptomatic HF patients show LV dilatation according to ESV and EDV.

Mechanical dyssynchrony

In healthy volunteers, mean SDI was 5.6 ± 3.6%, while in asymptomatic LBBB patients mean SDI was 7.3 ± 3.2%. No significant difference was observed between healthy volunteers and asymptomatic LBBB patients ($P = 0.08$). Symptomatic HF patients with a LBBB differed significantly from both other groups, with a mean SDI of 12.8 ± 4.8% (HF patients vs. healthy volunteers, $P < 0.0001$; HF patients vs. asymptomatic LBBB patients, $P = 0.001$) (see Table 2 and Figure 4). Between SDI and EF, an inverse correlation of $r = -0.719$ was observed.
Figure 5 shows the inverse correlation between SDI and EF. Asymptomatic LBBB patients compared to non-ischaemic cardiomyopathy patients with symptomatic HF and a LBBB

A subanalysis in which HF patients with an ischaemic cardiomyopathy were excluded, was performed. The remaining subgroup of symptomatic HF patients (n = 12, 4 male) was compared to the asymptomatic LBBB patients (n = 22, 12 male). The EF was 30 ± 10% in the non-ischaemic cardiomyopathy HF subgroup, which differed significantly from the asymptomatic LBBB patients (P = 0.001). ESV also showed a significant difference between asymptomatic LBBB patients and the HF subgroup (P = 0.025). Mechanical dyssynchrony in the asymptomatic LBBB group remained significantly different from the HF subgroup (P = 0.008). A SDI of 12.7 ± 3.7% was measured in the non-ischaemic cardiomyopathy HF subgroup. Table 3 shows an overview of the global LV function and SDI.

![Figure 3](image-url)
A cut-off value of SDI was determined by ROC curve analysis to assess the predictive value of this parameter for the presence of symptoms of HF. For SDI, a cut-off value of 10.8%, with a sensitivity of 69.6% and a specificity of 92.1%, was obtained for the presence of symptoms of HF.

**Reproducibility**

After a short learning curve, time needed for post-processing analysis of the RT3DE acquisitions was approximately 20 min per patient, independent of the person who was doing the analysis.

For intra-observer analysis of the RT3DE data, a sample of fifteen patients was re-analysed by observer JD in a period ranging from 1–2 weeks between first and second analysis. Bland-Altman measured intra-observer variability was good with a mean ± SD of 0.6 ± 2.9% for EF and 0 ± 3.8% for SDI. Intra-observer correlation coefficient and variability for EF were 0.980 and 1.1% and for SDI they were 0.729 and 1.5% respectively.

For the inter-observer reliability analysis of the RT3DE-data, five patients per studied group were randomly selected. There was an excellent correlation between the observers JD and PD for EF and SDI. Analysis of systematic bias showed a mean ± SD of 2.1 ± 5.0% for EF and 1.9 ± 2.5% for SDI. The inter-observer correlation coefficient and variability were 0.946 and 3.5% for EF and 0.834 and 6.7% for SDI.

**Discussion**

An important finding of this study is that RT3DE is useful for detecting differences in global LV function and mechanical dyssynchrony in asymptomatic LBBB patients, compared to healthy volunteers and symptomatic HF patients with a LBBB, who were age-matched and had mild differences in co-morbidity and the grade of mitral regurgitation. Assessment of global LV function demonstrated that patients...
with asymptomatic LBBB and patients with a symptomatic LBBB had a moderate and severe reduction in EF, respectively.

Mechanical dyssynchrony was easy to obtain and to reproduce with RT3DE and the post-processing software. In healthy volunteers, mild mechanical dyssynchrony was observed, in asymptomatic LBBB patients intermediate mechanical dyssynchrony was observed, although not significantly different from healthy volunteers, and in symptomatic LBBB patients, severe mechanical dyssynchrony was observed, which differed significantly from healthy volunteers and asymptomatic LBBB patients.

In a subanalysis, the SDI of the non-ischaemic subgroup of symptomatic HF patients remained significantly increased in relation to asymptomatic LBBB patients, as was already the case with the SDI between asymptomatic LBBB patients and the whole group of symptomatic HF patients. In this study, the measured amount of mechanical dyssynchrony in the symptomatic HF group might not have been influenced much by the aetiology of the cardiomyopathy, although detailed information about the amount of myocardial fibrosis is lacking.

As observed previously in other studies, the EF and the amount of mechanical dyssynchrony showed an inverse correlation. In accordance with results of a study by Vernooij et al., the trend to increased mechanical dyssynchrony in asymptomatic LBBB patients and the significant increased mechanical dyssynchrony in symptomatic LBBB patients in the present study, might be held responsible for the observed mild global LV dysfunction in asymptomatic LBBB patients and severe global LV dysfunction in symptomatic LBBB patients with similar QRS durations and co-morbidity. Thus, demonstrating that mechanical dyssynchrony might negatively affect LV function and the resulting symptomatic status.

The EF measured with RT3DE was lower than one would expect when conventional 2D echocardiography is used, especially in healthy volunteers. Minor deviations of measurements of RT3DE have already been recognized by other authors, who compared RT3DE to other imaging modalities as magnetic resonance imaging. Furthermore, as a systemic bias it still allows comparisons between the groups.

As in the current study the focus is on RT3DE measured global LV function and mechanical dyssynchrony in asymptomatic LBBB patients compared to healthy volunteers and symptomatic HF patients with a LBBB. Kapetanakis et al. were one of the first who used RT3DE for evaluation of mechanical dyssynchrony in healthy volunteers and HF patients with and without QRS prolongation. In HF patients with severe LV dysfunction (n = 44), they found a SDI of 15.7 ± 6.7%, which was in accordance with a SDI of 12.8 ± 4.8% in our HF patients (n = 23). Inter-observer variability and intra-observer variability were similar to our findings.

Another study evaluated mechanical dyssynchrony and global LV function when cardiac resynchronisation therapy was switched off. In a small group of HF patients (n = 13), SDI, based on 12 LV segments and measured in milliseconds, increased significantly from 43 ± 17 ms to 70 ± 22 ms and EF decreased from 38 ± 11% to 33 ± 10%. The results confirm the findings in the present study and indicate that an increased mechanical dyssynchrony is associated with a decrease in global LV function.

As our study focused on the effects of SDI in patients with a LBBB with and without symptoms of HF, patients with a small QRS duration and symptoms of HF have not been studied. Furthermore, others studied patients with a small QRS duration before. However, future studies will be necessary to find out if SDI is increased in those patients.

Clinical implications

With RT3DE evaluation of LBBB patients with and without symptoms of HF, differences in global LV function and mechanical dyssynchrony can be observed. The differences in mechanical dyssynchrony of both LBBB groups suggest that patients with a LBBB, who achieve a certain amount of mechanical dyssynchrony, may develop symptomatic HF. Therapeutic interventions that will decrease mechanical dyssynchrony may lead to a reduction of symptoms of HF.

Study limitations

In patients with a LBBB, it is often unknown for how long a LBBB has been present. The process of remodelling of the LV that might occur after the formation of a LBBB, may be more distinct in a patient with a long lasting LBBB, than in a patient with a new onset LBBB.

Another technical limitation of RT3DE is endocardial motion that might not reflect systematically myocardial contraction due to passive endocardial motion in, for example, ischaemic cardiomyopathy. However, as mentioned earlier, in a subanalysis, we excluded ischaemic cardiomyopathy patients and our main findings remained unchanged, although the numbers of patients in this subanalysis were low, with a consequent weakening of the statistical comparison.

In RT3DE, frame rates are relatively low (20–25 Hz) compared to tissue Doppler imaging (100–150 Hz). For evaluation of mechanical dyssynchrony, low frame rates can be a limitation in detecting very subtle dyssynchrony differences between the segments. However, RT3DE acquisitions have high spatial resolution and post-processing analysis can be done fast with good reproducibility, compared to other imaging techniques.

The presence of symptoms of HF might have been caused by other factors than SDI. Although care was taken not to include patients with disease states that could cause symptoms similar to HF, like pulmonary hypertension, some undiagnosed diseases might have been present in the study population. Furthermore, more mitral regurgitation was observed in the symptomatic group of LBBB patients.

Finally, the SDI cut-off value for the presence of symptoms of HF was derived from a relatively small number of patients, and should only be used as a suggestive value. In addition, the number of healthy volunteers (n = 16) may be relatively low for creating normal reference values.

Conclusions

RT3DE evaluation of age-matched asymptomatic LBBB patients, healthy volunteers and symptomatic HF patients with a LBBB showed that global LV function of asymptomatic LBBB patients already is slightly impaired compared to healthy volunteers. However, patients with HF and a LBBB have the most severely impaired LV function.
Although the observed difference is not significantly different, mechanical dyssynchrony in asymptomatic LBBB patients already is increased, compared to mechanical dyssynchrony in healthy volunteers. Patients with symptomatic HF and a LBBB have the most severe mechanical dyssynchrony. Quantification of mechanical dyssynchrony with RT3DE is useful, as increased mechanical dyssynchrony might have an effect on global LV dysfunction and consequential symptoms of HF. When a substantial level of LV mechanical dyssynchrony is reached, it might be suggestive for the presence of symptoms of HF.

References