Post-systolic shortening influences early diastolic filling in patients with dilated cardiomyopathy

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ABSTRACT

Background: We investigated whether post-systolic contraction has an impact on the diastolic function in patients with dilated cardiomyopathy (DCM).

Methods: Forty-eight DCM patients and 14 healthy volunteers underwent standard echocardiography, tissue Doppler imaging and strain focusing on diastolic function. The loops were recorded and post-systolic strain index (PSI) derived from speckle tracking strain analysis was assessed off-line.

Results: The post-systolic contraction was observed in 86% of the DCM patients.

In correlations of post-systolic strain index and individual diastolic parameters, mitral anulus velocity in early diastole (Ea) showed statistically significant relation ($r = -0.48$, $p = 0.001$) as well as the ratio of peak velocity of transmitral filling in early diastole and mitral anulus velocity in early diastole ($E/E_a$) ($r = 0.39$, $p = 0.012$).

Other assessed diastolic parameters did not reveal any significant correlations with PSI; peak velocity of transmitral filling in early (E) and late diastole (A), decelerating time of early diastolic filling (DT), mitral anulus velocity in late diastole (Aa).

Conclusion: There is a significant association between post-systolic shortening and a worsening of left ventricle (LV) diastolic filling in DCM patients.

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1. Background

Dilated cardiomyopathy (DCM) is a common form of heart muscle disease with an estimated prevalence of 1:2500, presenting the third most common cause of heart failure and the most frequent cause of heart transplantation [1].

The diastolic function in DCM patients plays an important role in their performance and diastolic dysfunction is linked to worse prognosis.

According to Pinamonti et al. not only the occurrence of diastolic dysfunction in DCM patients was associated to higher mortality rates, but also a persistence of diastolic dysfunction after 3 months of treatment was associated with higher mortality and urgent heart transplantation rates, as the persistence of diastolic dysfunction after treatment brought an additional prognostic information [2].

In the model suggested by Bruch et al., the prognosis of chronic heart failure patients depended mainly on left ventricle systolic diameter, QRS duration and diastolic function.

Moreover in patients with a wide QRS the prognosis was significantly worse in the presence of diastolic dysfunction than without it [3].

There are several echocardiography approaches that can be used to quantify left ventricle diastolic function, including deformation analysis.

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Recently used Doppler derived strain analysis showed many limitations, such as angle dependency and noise artifacts. The speckle tracking derived strain analysis based on the gray scale in 2D images does not have the limitation of angle dependency, and allows us to assess radial, circumferential and longitudinal strain, not being influenced by the tethering of adjacent segments [4].

The ventricle deformation can be resolved into three major components: the longitudinal, radial and circumferential.

Out of these three directions of ventricular deformation we chose to assess the longitudinal component, because it plays a major role in left ventricle diastolic function and performance [5,6].

Therefore the post-systolic contraction movement is either referred to as thickening when assessing the radial component of ventricle deformation or shortening for the longitudinal, as in our study.

Myocardial fibers responsible for longitudinal motion are placed close to subendocardium contrary to the circumferential mid wall myocardial fibers that provide the circumferential function.

The subendocardial fibers are more vulnerable to ischemia and fibrosis, which explains the impaired longitudinal function in condition of mechanical stress [7].

Post-systolic shortening (PSS) can be generally caused by delayed electrical activation, by neighboring segment interaction in dyskinetic segments or by structural changes in myocardium causing delayed contraction.

PSS is therefore observed in various diseases of the myocardium, including conduction abnormalities as in the presence of left or right bundle branch blocks, scored myocardium as a result of myocardial infarction, contractile abnormalities and fibrous tissue replacement as in cardio-myopathies, myocardial ischemia, metabolic disorders such as diabetes, in hypertension and in heart valve diseases [2].

We assume that the occurrence of contraction after the aortic valve closure, observed in this study as the PSS, worsens early diastolic filling.

The aim of this study was to assess the relation between PSS, quantified as the post-systolic strain index (PSI), and diastolic function in patients with dilated cardiomyopathy.

2. Methods

2.1. Subjects

Forty-eight DCM patients were examined from the year 2006 to 2009, together with 14 sex- and age-matched healthy controls.

The inclusion criteria were: sinus rhythm, no presence of coronary artery disease on coronary angiography, absence of acquired etiology of dilated cardiomyopathy.

All patients underwent standard complete echocardiography examination focusing on diastolic function, physical examination, routine biochemical and hematological blood tests, 12 lead ECG, chest X-ray.

All enrolled patients signed a written consent and the study was approved by the local ethics committee.

2.2. Echocardiography

Echocardiography examinations were performed using Vivid 7 (GE Milwaukee, WI) with a M3S transducer according to recommendations of the American Society of Echocardiography [8].

Three consecutive cardiac cycles were recorded for the evaluation of each parameter; the mean of all three cycles was used for data analyses.

Transmitral and aortic flows were recorded using conventional pulsed Doppler echocardiography. The sample volume with a fixed length of 5.1 mm was placed between the tips of mitral and aortic leaflets to obtain recordings of transmitral and aortic flows that were used to define individual phases of cardiac cycles, where aortic valve closure defines end of systole.

Left ventricle (LV) volumes and ejection fraction were calculated using modified Simpson’s rule.

From the transmitral pulsed Doppler flow the following parameters were assessed: peak early (E) and late (A) diastolic transmitral flow velocities, early filling deceleration time (DT), which was measured as a time interval from peak early mitral filling velocity to its deceleration to the baseline.

Pulsed-wave Doppler tissue imaging of mitral annular motion was recorded at septal and lateral annular corner, the mean of these two velocities was used for the analysis. The mitral annular velocities were assessed in early (Ea) and late (Aa) diastole.

The mitral and aortic leaflets to obtain recordings of transmitral and aortic flows that were used to define individual phases of cardiac cycles, where aortic valve closure defines end of systole.

The ratio of E/Ea was used to estimate the LV filling pressure [9].

2.3. Longitudinal strain analysis

The high spatial resolution variant of speckle tracking echocardiography was used for low deformation values expected in DCM patients. Two dimensional images were obtained at a frame rate of 44–82 frames per second (mean 69.5 ± 1.3). Apical 4- and 2-chamber views were stored and the recorded loops were digitally analyzed off line. For speckle tracking deformation analysis, we used software EchoPAC PC 6.1.0.b (GE Medical Systems, Horten, Norway). The LV endocardium was traced at end-systole in a click-to-point approach. Then, the software automatically outlined the myocardium between the endocardium and epicardium in all frames throughout the cardiac cycle. The myocardium in each echocardiography view was automatically divided into 6 predefined segments and the analysis of deformation for each segment throughout the cardiac cycle was performed. The mean deformation curve obtained as a mean of all segments was used for the analysis (Figs. 1 and 2).

The longitudinal strain data were expressed as a mean of the data from apical 4- and 2-chamber view.

The post-systolic strain index (PSI) was derived from the following equation: \( PSI = \frac{\text{peak strain} - \text{peak systolic strain}}{\text{peak systolic strain}} \).
Peak systolic strain was measured as the maximum value of strain in systole, which was defined as the time interval between the aortic valve opening and closure. The peak strain was defined as the maximum strain irrespective of its timing. (i.e. peak strain could represent post-systolic strain if occurred after the aortic valve closure or peak strain could be equal to peak systolic strain if occurred in systole.) Therefore the value of PSI in patients where post-systolic shortening was not present is zero.[10] The PSI different to zero means, that the peak strain occurred after the closure of the aortic valve.

Reproducibility of strain assessment was already stated in our previous work, comprising intra-observer variability up to 10% and inter-observer variability up to 10–15%.[11]

3. Statistical analysis

Variables in our data set showed normal distribution therefore parametric statistics were applied. The variables were described with mean and standard deviation, if not stated otherwise. Two independent groups in continuous variables were compared with T-Test for independent samples. To compare two groups in categorical variables the chi-square test or Fisher exact test was used.

If the compared groups did not show homogeneity of variance, non-parametric test (Mann Whitney U test) was used.

Correlations were assessed with Pearson correlation coefficient to determine linear relationship.

All results were considered statistically significant when \( p < 0.05 \).

Statistical analyses were performed using Statistica 7.0, StatSoft, Inc.

4. Results

Out of the total number of studied DCM patients (48), only 42 patients had complete applicable strain data for the analysis, in six patients the acoustic window was not good enough to perform speckle tracking analysis. One patient with extremely outlying strain values was excluded from the analysis.

Baseline characteristics of the patients are shown in Table 1.

There were no differences between groups except for hyperlipidaemia, hypertension and QRS width.

The results of echocardiography examination are in Table 2. DCM patients had significantly lower tissue Doppler velocities of mitral annulus in early and late diastole and a higher E/Ea ratio comparing to the healthy volunteer group, at the same time DCM patients had lower ejection fraction (EF) and higher left ventricle end diastolic volume indexed to body surface area (LVEDVi), which was of course expected.

The post-systolic shortening in healthy volunteers was zero, no healthy volunteer presented any LV post-systolic shortening.
shortening on the global strain curve, 34% of DCM patients presented PSI > 0.1.

The correlation of echocardiography parameters with PSI are presented in Table 3.

A statistically significant relationship was found between post-systolic strain index and Ea, E/Ea, LV ejection fraction, which are shown in Graphs 1–3.

Additionally the multivariate regression analysis for PSI index as dependent variable was performed with independent variables Ea, E/Ea, EF LK, QRS duration. Stepwise selection procedure selected only Ea as the independent prediction, (EF/LK is also a good predictor but worse Ea and due a strong correlation between Ea and EF/LK finally

### Table 2 – Echocardiography parameters in DCM patients and healthy controls. Data are represented as mean ± standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>DCM</th>
<th>Healthy volunteers</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSI</td>
<td>0.09±0.09</td>
<td>0</td>
<td>0.000000</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>25.8±8.5</td>
<td>62.9±4.0</td>
<td>0.000000</td>
</tr>
<tr>
<td>LVEDVi (ml/m2)</td>
<td>115.6±51.2</td>
<td>52.1±8.9</td>
<td>0.00024</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>79.6±22.0</td>
<td>84.8±11.8</td>
<td>NS</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>49.4±19.0</td>
<td>54.7±16.7</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>1.9±0.9</td>
<td>1.7±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>131.5±40.4</td>
<td>147.2±19.8</td>
<td>NS</td>
</tr>
<tr>
<td>Ea (cm/s)</td>
<td>6.4±2.3</td>
<td>12.4±2.6</td>
<td>0.000000</td>
</tr>
<tr>
<td>As (cm/s)</td>
<td>5.2±1.6</td>
<td>8.4±1.9</td>
<td>0.000000</td>
</tr>
<tr>
<td>E/Ea</td>
<td>13.4±4.9</td>
<td>7.1±1.5</td>
<td>0.00015</td>
</tr>
</tbody>
</table>

E = transmitral filling velocity in early diastole.
A = transmitral filling velocity in late diastole.
DT = time to deceleration of E.
Ea = mitral annulus velocity in early diastole.
As = mitral annulus velocity in late diastole.
LV EF = left ventricle ejection fraction.
LVEDVi = left ventricle end-diastolic volume indexed to body surface area.
PSI = post-systolic strain index.

### Table 3 – Correlation of echocardiography parameters with post-systolic strain index in DCM patients. “r” stands for Pearson correlation coefficient. Abbreviations as in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p-level</th>
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<tr>
<td>Diastolic parameters</td>
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<td></td>
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<tr>
<td>E (cm/s)</td>
<td>−0.03</td>
<td>NS</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>0.25</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>−0.18</td>
<td>NS</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>−0.12</td>
<td>NS</td>
</tr>
<tr>
<td>Ea (cm/s)</td>
<td>−0.48</td>
<td>0.001</td>
</tr>
<tr>
<td>As (cm/s)</td>
<td>−0.02</td>
<td>NS</td>
</tr>
<tr>
<td>E/Ea</td>
<td>0.39</td>
<td>0.012</td>
</tr>
<tr>
<td>Systolic parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>−0.45</td>
<td>0.003</td>
</tr>
<tr>
<td>LVEDVi ml/m2</td>
<td>0.31</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Graph 1 – Scatterplot of post-systolic strain index (PSI) against mitral annular velocity in early diastole (Ea) in (cm/s). $r = −0.48, p = 0.001$. Data present DCM patients only.

Graph 2 – Scatterplot of post-systolic strain index (PSI) against the ratio of transmitral flow in early diastole and mitral annular velocity in early diastole (E/Ea). $r = 0.39, p = 0.012$. Data present DCM patients only.

Graph 3 – Scatterplot of post-systolic strain index (PSI) against left ventricle ejection fraction LV EF (%). $r = −0.45, p = 0.003$. Data present DCM patients only.
explain the finding of post-systolic shortening in DCM patients. There are other related factors contributing to post-systolic contraction, which may play a role in the responsiveness to resynchronization therapy.

According to the previous works, the global post-systolic motion was found only occasionally in healthy controls. The global PSI values over 0.1 are considered pathological [10].

In our study the PSI values vary from 0.05 to 0.29 in DCM patients, and only 34% of our DCM patients present pathological PSI over 0.1.

Post-systolic shortening can occur in patients with hypertension and diabetes without other disease of the myocardium, which could cause bias in our sample, because none of our healthy volunteers suffered any of these diseases, but at the same time there was no association between occurrence of hypertension or diabetes or both and the value of PSI in DCM patients.

PSI has been studied in coronary artery disease, both with Doppler derived strain and magnetic resonance derived strain, in both animal experiments and clinical studies.

Post-systolic shortening was observed in 80% of coronary artery disease patients [12].

PSI has been shown as a marker of viability during dobutamine echocardiography [13].

Assessment of post-systolic thickening may be valuable to detect myocardial ischemia memory, where PSI is more sensitive marker of ischemia than peak systolic strain [14].

There was a significant post-systolic radial strain decrease at the moment of balloon inflation in the coronary vessel in both normo- and hypo- or akinetic segments in patients undergoing coronary angioplasty, comparing to the values at baseline [15].

Therefore, PSI was suggested as a method for indentifying acutely ischemic myocardium.

The ratio of post-systolic strain to total strain can even differentiate between levels of ischemia in animal experiment [16].

There is a discussion whether post-systolic movement is caused by passive recoil due to wall dyskinesia or if it is an active movement – post-systolic contraction – caused by delayed contraction.

This was studied closer in animal experiments in ischemic heart disease, coming to a conclusion, that in dyskinetic segments it is a passive mechanism due to the interference with neighboring non-ischemic segments, while in akinetic or hypokinetic segments it is a marker of actively contracting myocardium [17].

This theory was confirmed by clinical magnetic resonance study where the post-systolic deformation was present in a transmural scar tissue [18].

According to the study by Ring et al., the post-systolic contraction in patients with heart failure is a result of LV asynchronous contraction [19]. The post-systolic motion was linked with QRS duration, where QRS >0.12 was a marker of elevated PSI (19), which is partially in agreement with our study. In our group of patients the magnitude of PSI can be attributed to conduction delay in patients with prolonged QRS, and also to fibrous tissue replacement, since prolonged QRS does not fully explain the appearance of post-systolic shortening in our patients. The myocardial ischemia in our
patients is very unlikely, since coronary artery disease was excluded. Therefore we assume the PSI to be an active movement in our patients.

6. Limitation of the study

Due to the typical echocardiography image of a dilated heart in DCM patients it was not possible to perform blind analysis of echocardiography data.

The healthy volunteer group was relatively small and may not have been representative of the population, as many of the volunteers were found among the employees of the hospital. Another limitation is the lack of clinical data of our patients, such as NT pro BNP, which would be interesting in relation to the post-systolic shortening.

An additional limiting factor of our study is the lack of follow up which could help us decide whether post-systolic shortening is linked to worse prognosis in DCM patients.

7. Conclusion

The post-systolic shortening in DCM patients is associated with the worsening of early diastolic filling. This disturbance may be an important therapeutic target in the management of DCM patients in the future. Whether post-systolic shortening is connected with severity of clinical symptoms of heart failure in patients with dilated cardiomyopathy, remains to be further investigated.

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