Clinical Research

Prevalence of left ventricular dyssynchrony in patients with heart failure assessed by a novel programmer-cardioGRAF

Can-Zhan Zhu1, Naoto Takahashi2, Akira Yamamoto2, Masahira Ishikawa2, Naomi Kawaguchi2, Takahiro Uchida2, Kazuo Munakata2

1. Department of Cardiology, 2nd Hospital of Xi’an Jiaotong University, Xi’an, China
2. Internal Medicine, Radiology Department, Nippon Medical School Musashikosugi Hospital

Objectives  Left ventricular systolic dyssynchrony is the most important determinant of response to cardiac resynchronization therapy (CRT), playing a vital role to predict improvement of systolic function or LV reverse remodeling. CardioGRAF is a novel programmer based on the ECG gated single photon emission computed tomography (G-SPECT) imaging to detect LV systolic and diastolic dyssynchrony simultaneously. This study was to investigate the prevalence of systolic and diastolic left ventricular (LV) dyssynchrony in patients with heart failure. Methods  We retrospectively studied 69 patients with heart disease, including 31 patients who had symptoms of heart failure (NYHA class II - III), and 38 patients who had no symptoms of heart failure (NYHA class I). G-SPECT data were analyzed by cardioGRAF, and measurements included the time to end systole (TES), the time to peak ejection (TPE), the time to peak filling (TPF), TES+TPF and maximal difference (MD) of each parameters were obtained. Using the 95th percentile of the control group as a cutoff of 150 ms for MD-TES, 139 ms for MD-TPE, 345 ms for MD-TPF and 315 ms for MD-TES+TPF.

Results  The prevalence of LV systolic dyssynchrony was significantly higher in heart failure patients with reduced LV ejection fraction (LVEF)<45% (72% for MD-TES; 64% for MD-TPE) compared with heart failure patients with preserved LVEF=45% (14% for both MD-TES and MD-TPE; P=0.002, P=0.005, respectively); The prevalence of MD-TES<150 ms was higher in NYHA class III patients (64%) compared with NYHA class II patients (27%, P=0.049). However, the prevalence of the LV diastolic dyssynchrony were high but not difference between NYHA class III patients (97%) and NYHA class II patients (91%, P=0.69); and class III(96%) and class II(96%) patients as well as both patients with preserved LVEF (43% for both MD-TDF and MD-TES+TPF) and patients with reduced LVEF(46% for MD-TDF; 72% for MD-TES+TPF; P=NS). Conclusions  The prevalence of LV systolic dyssynchrony was high in heart failure patients with reduced LVEF. Diastolic dyssynchrony was common in patients with heart failure. CardioGRAF maybe a useful method to detect LV dyssynchrony (J Geriatr Cardiol 2009; 6:151-156).

Key words  dyssynchrony; heart failure; cardioGRAF; single photon emission computed tomography

Introduction

Cardiac resynchronization therapy (CRT) has been proven unequivocally beneficial for patients with advanced chronic heart failure (HF) with prolonged QRS complexes.1-3 Despite enthusiasm of giving this therapy to patients who fulfilled the current recommendation, nonresponse was observed in about one-third of patients who may not show clinical or left ventricular (LV) reverse remodeling response,2,4,5 emphasizing the need for additional selection criteria. Several studies have shown that the main predictor of response to CRT may be the presence of intra-LV dyssynchrony.6,7 Recent studies have suggested the vital role of assessing systolic dyssynchrony by echocardiography to predict improvement of systolic function or LV reverse remodeling.4,5 But dyssynchrony assessed by echocardiography was only between the septum and lateral wall, not among the whole regions of LV. In order to evaluate the dyssynchrony of the entire LV, we developed a novel programmer-cardioGRAF, it can detect systolic and diastolic dyssynchrony among every segment of LV simultaneously based on ECG gated SPECT data.

The aim of the present study is to investigate the prevalence of LV intraventricular systolic and diastolic dyssynchrony in patients with heart failure and compare the findings with those of patients with heart disease and no symptoms of heart failure using the novel programmer-cardioGRAF.

Methods

Study population
This retrospective study consisted of 69 subjects.
Those patients belonged to New York Heart Association (NYHA) class I serves as control group, including 38 patients. The others were the study group, including 31 patients, divided into 2 groups according their NYHA classifications: NYHA II group and NYHA III group. Patients with heart failure were also divided according their LV ejection fraction (LVEF) into those with preserved LVEF (≥45%) and those with reduced LVEF (<45%).

**ECG gated single photon emission computed tomography (G-SPECT)**

A single dose of technetium-99m sestamibi (600MBq) was administrated intravenously at rest. G-SPECT was initiated 30-60 minutes after tracer injection. We used a parallel dual head gamma camera (HITACHI RW 2600i, HITACHI Corporation, Tokyo, Japan) equipped with low-energy high resolution collimators. Sixty-four projections (40-50 beats/projection) were obtained over a 360° circular orbit. Acquisition was gated for 8 frames/cardiac cycle with bad beat rejection. Images were reconstructed using filtered back projection.

**pFAST**

Perfusion and function assessment for G-SPECT(pFAST) ver.2.4.2, developed in Sapporo Medical University, Hokkaido, Japan, was used for detection of endocardial surface.

**CardioGRAF**

Cardio gated SPECT regional assessment for left ventricular Function was developed in Nippon Medical School Musashikosugi Hospital, Kawasaki, Japan.

Time volume curves (TVC) with it’s first derivative curves (FDC) for both the global or regional 17 segments were made by acquired data with 8 frames/cardiac cycle using Fourier transform in this study. CardioGRAF programmer can calculate many parameters. Usually, those parameters can be divided into two groups: systolic parameters and diastolic parameters. There are three parameters used in this study. They are regional time to end systole (rTES), regional time to peak ejection rate (rTPE), regional time to peak filling rate (rTFR), as showed in Fig.1. After those parameter’s value were taken, we can calculate the novel index, maximal difference of segmental value marked as MD, by subtracting minimal value from maximal value. MD means maximal time lag among the 17 segments of same parameter, as showed in Fig.2.

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**Fig.1 The main window of cardioGRAF.** The left side shows the time volume curve (TVC) and it’s first derivative curve (FDC). The horizontal axis represents cardiac cycle, the upper vertical axis represents LV volume expressed as percentage of LV volume, the lower vertical axis represents LV volume change rate expressed as LV volume per second. The lowest point of TVC represent the end of systole, so from beginning to this point is the time to end of systole, TES, marked as T1; The lowest point of FDC, corresponding to peak ejection rate, so from beginning to this point is the time to peak ejection rate, TPE, marked as TD1; The peak point of FDC, corresponding to peak filling rate, from the lowest point of TVC to this point is the time to peak filling rate, TPF, marked as TD2. The right upper corner is the check panel; the polar map represents 17 LV segments. The parameter’s value was given at the right lower corner. If you click on this button, you can check the curves of every region, and the value was given automatically.
Fig. 2  Schematic diagram of MD measurement. The left side shows the time volume curve (TVC) and its first derivative curve (FDC) of 17 LV segments, the vertical dotted line represents TPE, TES and TES+TPF of each segment respectively. The right upper panel is the LV segmentation; the lower is the definition of MD and the calculation. The MD of TPF could not show on the diagram.

Statistical analysis
The Statistical Package for Social Sciences, version 12.0 (SPSS, Chicago, Illinois) was used for statistical analysis. Data were presented as means ± SDs or total number (percentages). Also, the 75th and 95th percentile for the values in the control subjects are given. The unpaired t tests and Mann-Whitney test were used, as appropriate. Intra- and inter-observer variability was determined by the coefficients of variance by comparing the SD of the test differences as the percentage of the average in the 2 series. Statistical significance was defined at P<0.05.

Results

Population characteristics
A total of 69 subjects were retrospectively studied: 38 NYHA class I patients serve as controls and 31 patients with heart failure belong to the study group. The controls (61% men) were an average age of 57±14 years and had a mean LVEF of 69% ± 8%. Table 1 lists the clinical characteristics of the patients with heart failure divided into 4 groups according to LVEF and NYHA classification.

Reproducibility of cardioGRAF parameters measurements
The intraserver variability was 4.3% for rTTE, 8.7% for rTPE, 9.4% for rTPF, and 4.0% for rTES+TPF. The interobserver variability was 6.7% for rTTE, 12.5% for rTPE, 13.3% for rTPF, and 7.2% for rTES+TPF.

Measurements of LV systolic and diastolic dysynchrony
The values of NYHA class I patients are listed in Table 2. The linear regression analysis result shows that there is a mild to moderate positive relationship between aging and MD of TES (r=0.336, P=0.039), TPF (r=0.453, P=0.004) and TES+TPF (r=0.364, P=0.025); interestingly, aging is not related with MD of TPE (r=0.271, P=0.100). As to the heart failure group, there are no relationship between MD and aging, not only the systolic parameters, but also the diastolic parameters.

The results for patients with heart failure according to NYHA class and LVEF are listed in Table 3. The result shows that SPECT dyssynchrony parameters MD were not related to age.

Prevalence of LV dyssynchrony
The prevalence of MD-TES>150 ms was higher in NYHA class I patients (10 of 16 patients, 64%) compared with NYHA class I patients (4 of 15 patients, 27%, P=0.049). However, the prevalence of MD-TPE>139 ms was also higher in NYHA class I patients (9 of 16 patients, 56%) compared with that in NYHA class II patients (4 of 15 patients, 27%, P=0.101), but did not reach statistical significance. The prevalence of LV systolic dysynchrony was significantly higher in heart failure patients with reduced LVEF (12 of 17 patients, 72% for MD-TES; 11 of 17 patents, 64% for MD-TPE) compared with that in heart failure patients with preserved LVEF (2 of 14 patients, 14% for both MD-TES and MD-TPE; P=0.002, P=0.005, respectively); Figure 3 shows the prevalence of LV systolic dyssynchrony according to NYHA classification and LVEF. However, the prevalence of the LV diastolic dyssynchrony parameters MD-TPF and MD-TES+TPF were high without difference between NYHA
### Table 1  Clinical characteristics of patients according to NYHA class and LVEF

<table>
<thead>
<tr>
<th>Variable</th>
<th>NYHA I (n=38)</th>
<th>NYHA II (n=15)</th>
<th>NYHA III (n=16)</th>
<th>LVEF ≥ 45% (n=14)</th>
<th>LVEF&lt;45% (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>57 ± 14</td>
<td>65 ± 14</td>
<td>65 ± 16</td>
<td>66 ± 11</td>
<td>64 ± 18</td>
</tr>
<tr>
<td>Men(%)</td>
<td>61</td>
<td>53</td>
<td>69</td>
<td>64</td>
<td>71</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>69 ± 8</td>
<td>58 ± 15</td>
<td>41 ± 15</td>
<td>65 ± 9</td>
<td>37 ± 9</td>
</tr>
<tr>
<td>Ischemic heart disease(%)</td>
<td>29</td>
<td>47</td>
<td>25</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>Dilated cardiomyopathy(%)</td>
<td>5</td>
<td>3</td>
<td>38</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>Vavular heart disease(%)</td>
<td>11</td>
<td>20</td>
<td>31</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Other heart disease(%)</td>
<td>55</td>
<td>20</td>
<td>6</td>
<td>21</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 2  Control group values of cardioGRAF dyssynchrony parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Means±SD</th>
<th>75th percentile</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD-TES</td>
<td>85±38</td>
<td>116</td>
<td>150</td>
</tr>
<tr>
<td>MD-TPE</td>
<td>81±33</td>
<td>98</td>
<td>139</td>
</tr>
<tr>
<td>MD-TPF</td>
<td>164±99</td>
<td>241</td>
<td>345</td>
</tr>
<tr>
<td>MD-TES+TPF</td>
<td>139±93</td>
<td>184</td>
<td>315</td>
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</tbody>
</table>

### Table 3  cardioGRAF parameters of dyssynchrony according to NYHA class and LVEF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NYHA II (n=15)</th>
<th>NYHA III (n=16)</th>
<th>P value</th>
<th>LVEF=45% (n=14)</th>
<th>LVEF&lt;45% (n=17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD-TES</td>
<td>139±67</td>
<td>207±125</td>
<td>0.074</td>
<td>129±68</td>
<td>211±118</td>
<td>0.028</td>
</tr>
<tr>
<td>MD-TPE</td>
<td>119±63</td>
<td>254±202</td>
<td>0.020</td>
<td>127±149</td>
<td>239±163</td>
<td>0.058</td>
</tr>
<tr>
<td>MD-TPF</td>
<td>335±154</td>
<td>441±215</td>
<td>0.127</td>
<td>316±163</td>
<td>450±198</td>
<td>0.052</td>
</tr>
<tr>
<td>MD-TES+TPF</td>
<td>326±160</td>
<td>420±164</td>
<td>0.118</td>
<td>303±163</td>
<td>434±147</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Discussion

Because of the limited resolution of myocardial perfusion imaging with SPECT, it is not possible to measure the wall thickness of the left ventricle by geometric methods.\(^{11}\) However, the linearity between the change in myocardial wall thickness and the change in maximum counts extracted from the same myocardial region makes it possible to measure LV wall thickening via an G-SPECT acquisition.\(^{11}\) Count-based methods of measuring wall thickening have been applied to technetium-99m sestamibi ECG-gated planar studies,\(^{12-16}\) and have been validated by several investigators. Tc-99m ECG-gated planar studies have been used by Marcassa et al\(^{12}\) to show that count-based systolic wall thickening (SWT), measured in 10 normal volunteers, correlated very well with geometric methods applied to both computed tomography and magnetic resonance imaging. Marzullo et al\(^{13}\) showed good agreement (88%) between count-based SWT and wall motion measured by contrast ventriculography. Pace et al\(^{16}\) demonstrated that count-based SWT improved in 6 of 6 patients who underwent angioplasty. Kahn et al,\(^{17}\) using Tc-99m G-SPECT, found that semiquantitative assessment of SWT correctly identified 29 of 31 reversible perfusion defects. These count-based methods were based on the same observation that a change in wall thickness is directly proportional to a change in counts throughout the cardiac cycle.\(^{11}\) It has been shown that the proportionality is better maintained when imaging with a spatial resolution that is low compared with myocardial wall thickness, as well as when measuring SWT in relatively uniform regions of the myocardium.\(^{10,12}\) Chen et al\(^{20}\) using phase analysis method.

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**Note:** The provided text includes various clinical and scientific details, which are presented in a structured format using tables and figures. The content is primarily related to the clinical characteristics of patients according to NYHA class and LVEF, as well as the control group values of cardioGRAF dyssynchrony parameters. The discussion section highlights the limitations of myocardial perfusion imaging with SPECT, the correlation between count-based systolic wall thickening and geometric methods, and the validation of count-based methods using Tc-99m ECG-gated planar studies and Tc-99m G-SPECT.
to determine the onset of left ventricular mechanical contraction based on ECG-gated myocardial perfusion SPECT data in patients undergoing CRT, the results showed that the phase histogram of the patient before CRT was much wider and less peaked compared with the phase histogram after CRT. Dynamic onset of mechanical contraction (OMC) displays also showed that the wave of LV OMC of the patient before CRT was much more irregular and slower than that after CRT. It indicated that the post-CRT phase distribution was closer to the normal distribution than before CRT, implying improved LV mechanical synchrony of the patient after CRT.

Using cardioGRAF analysis of the G-SPECT imaging data, the main findings of our study were as follows. The prevalence of LV systolic dyssynchrony was high in patients with heart failure and reduced LVEF (72% for MD-TES, 64% for MD-TPE), whereas it was low in patients with heart failure and preserved LVEF (14% for MD-TES as well as for MD-TPE). However, The prevalence of LV diastolic dyssynchrony was common in all heart failure patients (from 43% to 64% for MD-TPF and from 43% to 72% for MD-TES+TPF).

As much as 30% to 40% of all patients with heart failure symptoms have a normal or slightly reduced LVEF. Also, in our study, the prevalence of heart failure with preserved LVEF was high (14 of 31 patients, 45%). Although the mortality rate of these patients is lower, their hospitalization rate for heart failure is comparable to that of patients with heart failure with reduced LVEF.21-22 To the best of our knowledge, few studies have been published on the prevalence of LV systolic and diastolic dyssynchrony in these patients.

The prevalence of LV systolic dyssynchrony was 14% in patients with heart failure with preserved LVEF, similar to prevalence detected by echocardiography using pulse-wave tissue Doppler imaging. Using the 95th percentile as a cutoff of 150 ms for MD-TES and 139 ms for MD-TPE, our prevalence of LV dyssynchrony in patients with heart failure with a reduced LVEF was 64-72%, similar to the prevalence of 57% in the study by Penicka et al.,23 61% by Bax et al.24 But it was higher than the prevalence of 46% report by Sutter et al.25 The differences in the incidence of LV dyssynchrony in the various studies may be related to differences in study population but also to methods and analysis of echocardiographic data; in particular, the definition of substantial LV dyssynchrony varied among the studies.26-28 In particular, in the present study, dyssynchrony among the whole left ventricular regions was evaluated, whereas in other studies dyssynchrony was assessed only between the septum and lateral wall.

Our 95th percentiles in controls of 150 ms for MD-TES and 139 ms for MD-TPE is close to the suggested cutoff of 130 ms for septal to posterior wall motion delay (SPWMD) detected by echocardiography. Pitzalis et al.14 proposed a simple M-mode parameter, the SPWMD, as a marker for intraventricular asynchrony. A prolonged SPWMD (>130 ms) was a predictor of clinical benefit and remodeling with biventricular pacing.29 More recently, measurements of electromechanical delays using pulswave TDI in 4 basal segments with calculation of the dispersion has been proposed as a marker of intraventricular dyssynchrony. Penicka et al.24 showed that this parameter was the best predictive parameter of reverse remodeling in 49 patients with heart failure with a wide QRS treated with biventricular pacing.

The prevalence of the diastolic intraventricular dyssynchrony is high in heart failure patients from 43% to 64% for MD-TPF and from 43% to 72% for MD-TES+TPF, similar to the prevalence of 46% in the narrow QRS group and 69% in the wide QRS group of heart failure patients in the study by Yu et al.2 and there was no difference between NYHA class II and class III patients as well as between patients with preserved LVEF and patients with reduced LVEF, implied that diastolic dyssynchrony was priority to the systolic dyssynchrony.

Our study had some limitations. First, our study has a smaller subjects population and a relatively large SD. The control group was also the patients with heart disease, not the health person. Second limitation of this study is that only 8 gates were used in the acquisition and sequential wall thickening patterns during the cardiac cycle with high temporal resolution were not obtained. The third one is that those time interval parameters were mainly affected by cardiac cycle length. Unfortunately till now, we could not find an effective method to correct those parameters.

CardioGRAF maybe a useful method to detect LV dyssynchrony. But it is required to compare with other modalities such as Speckle Tracking Image,30 to evaluate the accuracy and the sensitivity of cardioGRAF. Prospective clinical trials are also needed to validate whether this tool can be used to select patients with severe heart failure symptoms who might benefit from cardiac resynchronization therapy.

Reference


