Left ventricular diastolic function and cardiac disease
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2000

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Quantification of the atrial contribution to diastolic filling during radionuclide angiography

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Summary

In order to define exactly the onset of late diastolic filling with respect to atrial contraction, atrial contribution (AC) to left ventricular filling was quantified in 34 patients with a variety of diseases using radionuclide angiography. From the time-activity curve and its first derivative, a flow-volume loop was constructed. Using the flow-volume loop, the period between minimal flow and the moment of maximal end-diastolic counts was defined as AC-interval and correlated with the PQ-interval on the electrocardiogram. The relative filling volumes within these time periods were very closely related in all patients (r=0.99, p<0.0001). Also, the correlation between PQ-interval and AC-interval was statistically significant (r=0.82, p<0.0001). In a subset of patients PQ-interval and AC-interval were not exactly the same. In these patients, AC-interval was always longer than PQ-interval, indicating the existence of passive diastasis flow before the onset of atrial contraction. In patients with low heart rates this was more apparent than at higher heart rates. Despite the close relation of the PQ-interval on the electrocardiogram and the AC-interval of the flow-volume loop, they may represent different entities. In radionuclide angiography, the PQ-interval is therefore a better parameter to define the moment of onset of atrial activity than the AC-interval.

Nuclear Medicine Communications 1997;18:642-647
n the non-invasive assessment of diastolic left ventricular function, the quantification of the parameters of both early and late diastolic filling play an important role.\textsuperscript{1,2,3,4,5} The parameters of late diastolic filling are not only related to atrial contraction, but also to left ventricular relaxation and compliance. Various radionuclide angiographic and echocardiographic methods can be used to measure the volume displacement during atrial contraction.\textsuperscript{2,3,6,7,8} The moment of onset of atrial contraction is mostly determined by the shape of the measured curves.\textsuperscript{4,7,8,10,11,12,13} The use of an external reference point has not been applied to verify the exact duration of atrial contraction.\textsuperscript{9} We incorporated the PQ-interval of the electrocardiogram into the flow-volume loop as derived from the radionuclide time-activity curve of the left ventricle to define the onset of atrial contraction and separate this from late diastolic passive filling. The atrial contribution to left ventricular filling was thus quantified.

**METHODS**

**Patients.** Thirty-four patients participated in the study. Baseline characteristics of these patients are presented in Table 4.1. Twelve patients (35%) were normal, 4 patients (12%) had coronary artery disease, and 18 patients (53%) had other underlying disease. No patients had clinically significant mitral valve disease or aortic regurgitation. All patients were in regular sinus rhythm.

**Radionuclide Angiography.** In vivo labeling of red blood cells was performed by intravenous injection of $^{99m}$Tc-pertechnetate (20-30 mCi), 30 minutes after the intravenous administration of pyrophosphate. Image acquisition was obtained by a gamma camera (Siemens Orbiter) with an all-purpose parallel-hole collimator interfaced with a Pinnacle computer (Medasys Inc, Ann Arbor, Mich.). The gamma camera was positioned in the left anterior oblique view with a caudal tilt to optimally obtain separation of the left and right ventricle. The acquisition was gated to the QRS-complex of the electrocardiogram. To minimize count fall-off at the end of the cardiac cycle in the forward gated data, only a 5% cycle-length-window was accepted.\textsuperscript{14} Acquisition was completed after 150,000 counts per frame of 20 msec duration. The region of background correction was selected manually.\textsuperscript{15} After temporal smoothing with a five-harmonic Fourier fit of the raw data radionuclide time-activity curves of the left ventricle were generated from the cardiac images.\textsuperscript{16}

<table>
<thead>
<tr>
<th>TABLE 4.1. Baseline characteristics of the 34 patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (years)</td>
</tr>
<tr>
<td><strong>Sex</strong> (male/female)</td>
</tr>
<tr>
<td><strong>Previous history:</strong></td>
</tr>
<tr>
<td>No CAD (normal CAG)</td>
</tr>
<tr>
<td>CAD</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CAG = coronary angiogram.

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\textsuperscript{114} Acquisition was completed after 150,000 counts per frame of 20 msec duration. The region of background correction was selected manually.\textsuperscript{15} After temporal smoothing with a five-harmonic Fourier fit of the raw data radionuclide time-activity curves of the left ventricle were generated from the cardiac images.\textsuperscript{16}
Radionuclide image analysis. From the time-activity curve of the left ventricle the first derivative curve (time-flow curve) and then a flow-volume loop were constructed (Figures 4.1A and 4.1B). Both flow and volume are expressed as fractions of their maximal value during one cycle. The flow-volume loop is thus largely independent of the absolute flow and volume parameters and ejection fraction. The plot of flow against volume describes their relationship throughout the cardiac cycle. It can therefore be used to study the relative volume portions of early and late diastolic filling. Electro-mechanical delays as well as gating delays were accounted for by moving the time-activity curves so that end-diastolic counts coincided with the beginning of the QRS-complex on the electrocardiogram.

Measurements. Left ventricular ejection fraction (LVEF) was automatically determined with help of the time-activity curve. Atrial contraction time (AC-interval) was defined as the time interval between the diastasis point and the moment of maximal counts (being end-diastole). The diastasis point was found graphically in the flow-volume loop by aid of the computer, as it is represented by the lowest flow point between early and late diastolic filling. The moment of maximal counts was found analytically.

The PQ-interval was measured during data acquisition from an electrocardiographic rhythm strip by two observers with aid of a magnifying-glass and calibration scale. The PQ-interval was then plotted into the flow-volume loop. This was used to define two subgroups: A) patients in which AC-interval and PQ-interval were approximately the same (difference of < 10 msec) and B) patients in which AC-interval and PQ-interval differed ≥ 10 msec (Figure 1B).

**FIGURE 4.1A.** Left ventricular time-activity curve and first derivative (time-flow curve) of study no. 31 without compensation for gating and electro-mechanical delays. After early diastolic filling (EDF), the flow diminishes in the diastasis (D). Late diastolic filling (LDF) is a composition of passive flow and atrial contraction. EDV = end diastolic volume. **B.** Flow-volume loop of study no. 31. The PQ-interval (PQ) is measured on the electrocardiogram and the AC-interval (AC) is measured in the flow-volume loop. Here, AC-interval is longer than PQ-interval, probably due to passive filling before the onset of atrial contraction.
The relative contribution of late diastolic filling to total diastolic filling was then determined by using both AC-interval and PQ-interval as a reference point (AC% and PQ%). These relative volume portions were automatically calculated by the computer by integration of the Fourier function.

**Statistical analysis.** Measured data are presented as mean ± 1 standard deviation (SD) unless otherwise stated. Comparison of the baseline characteristics and the radionuclide angiographic results between the subgroups was performed with Student’s t test. For the correlations between the parameters of relative contribution of late diastolic filling to total diastolic filling and atrial contraction duration the Pearson correlation was used. To evaluate that AC-interval was always longer than PQ-interval, and never shorter, a sign-test was used. A test for declining probabilities was used to evaluate the chance of AC-interval to exceed PQ-interval in relation with heart rate.

**RESULTS**

**Analysis of all patients.** A scatter diagram for the relation between PQ-interval and AC-interval is presented in Figure 4.2 ($r=0.82$, $p=0.0001$). AC% and PQ% were also

**FIGURE 4.2.** Scatter diagram showing the relation of the PQ-interval on the electrocardiogram and the AC-interval in the flow-volume loop. Since a subset of 11 patients had a longer AC-interval than PQ-interval, the linear regression line for all the 34 patients was shifted upward from the line: AC-interval = PQ-interval.

**FIGURE 4.3.** Scatter diagram showing the relation of the PQ-interval on the electrocardiogram and the AC-interval in the flow-volume loop. Since a subset of 11 patients had a longer AC-interval than PQ-interval, the linear regression line for all the 34 patients was shifted upward from the line: AC-interval = PQ-interval.

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All patients: $r=0.995$, $p<0.0001$
very closely related (Figure 4.3: $r=0.99$, $p<0.0001$). Weak but statistically significant correlations were found between all measured late diastolic filling parameters (PQ-interval, AC-interval, PQ% and AC%) and heart rate ($r=0.43$ to $0.66$, $p<0.05$). A positive correlation existed also between the atrial filling fractions, AC% and PQ%, and age ($r=0.54$ and 0.53 respectively, $p<0.05$). No correlations were found with LVEF or with the other baseline characteristics.

**Subgroup analysis.** In a subset of patients, AC-interval was longer than PQ-interval, but never shorter (sign-test $p<0.01$). In Table 4.2 the baseline characteristics and the radionuclide angiographic data of this subgroup are compared to the subgroup in which AC-interval and PQ-interval were equal. Heart rate was the only statistically significant

**TABLE 4.2.** Comparison of the baseline characteristics and the findings between the subgroups at radionuclide angiography (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>PQ-interval = AC-interval (Group A)</th>
<th>AC-interval &gt; PQ-interval (Group B)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>43/57%</td>
<td>64/36%</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 14</td>
<td>61 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF</td>
<td>66 ± 12</td>
<td>62 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>HR</td>
<td>67 ± 10</td>
<td>60 ± 8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>15 (65%)</td>
<td>8 (73%)</td>
<td>NS</td>
</tr>
<tr>
<td>Medication:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>6 (26%)</td>
<td>4 (36%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ca$^{2+}$ channel blockers</td>
<td>3 (13%)</td>
<td>1 (9%)</td>
<td>NS</td>
</tr>
<tr>
<td>PQ-interval</td>
<td>177 ± 30</td>
<td>164 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>AC-interval</td>
<td>177 ± 30</td>
<td>189 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>PQ%</td>
<td>31 ± 11</td>
<td>27 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>AC%</td>
<td>31 ± 11</td>
<td>28 ± 8</td>
<td>NS</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; HR = heart rate; PQ-interval = PQ-interval on the electrocardiogram; AC-interval = atrial contraction time measured in the flow-volume loop; PQ% = volume displacement during atrial contraction using the PQ-time as reference point; AC% = id. using AC-interval as reference point.

**FIGURE 4.4.** Histogram showing the number of patients in each heart rate range of 10 bpm. The patients with different values for AC-interval and PQ-interval had relatively slow heart rates ($p<0.05$).
parameter in which the subgroups differed. It ranged from 51 to 85 beats per minute (35 to 59 frames) in group A, and from 43 to 78 beats per minute (38 to 69 frames) in group B (p<0.05). In group B there was no correlation between heart rate and the magnitude of the difference between AC-interval and PQ-interval. In Figure 4.4 a frequency distribution of the patients of both subgroups is presented for each heart rate interval of 10 bpm. The probability that AC-interval exceeded PQ-interval increased with lowering heart rates (p<0.01). In 55 percent of the patients with heart rates < 60 beats per minute AC-interval exceeded PQ-interval. In 82 percent of the patients with AC-interval exceeding PQ-interval, heart rate was < 65 beats per minute.

DISCUSSION
In this study we compared two radionuclide angiographic methods to quantify atrial contribution to diastolic filling using flow-volume loops. Both the PQ-interval on the electrocardiogram and the AC-interval on the flow-volume loop were used to define the onset of atrial contraction. Using the flow-volume loop, the relative volume portions of late diastolic filling (AC% and PQ%) rather than the absolute filling rates were calculated.\(^2,17,18\) Both these parameters correlated well. In a subset of patients with lower heart rates AC-interval however exceeded PQ-interval.

Previous measurements of atrial contribution to ventricular filling by radionuclide angiography. The assessment of late diastolic filling parameters by radionuclide blood pool scintigraphy has been established previously.\(^2,4,9,17,18\) Green et al. described a method using flow-volume loops.\(^17,18\) They assumed that the temporal component of electrical atrial activity to ventricular activity equals that of the subsequent mechanical activity. Bonow et al. corrected their time-activity curve for gating delays.\(^4,9\) They also used the PQ interval to define the moment of onset of atrial contraction. Electrico-mechanical delay was standardized to 40 ms. Arora et al. on the other hand used the diastasis point in the flow-volume loop to define the moment of onset of atrial activity.\(^2\)

Echocardiographic measurement of atrial function. Late diastolic filling parameters can also be obtained with Doppler echocardiography.\(^10,11,19,20,21,22\) With this approach, the volume displacement during atrial contraction can indirectly be measured by integration of the early and late transmitral flow velocity curve and calculation of this ratio.\(^11\) However, a filter is used to eliminate the low frequency signal. The measurement of the duration of late diastolic filling may then become inaccurate since the presence of a diastasis flow might be overlooked.\(^5,10,20,21\)

The correlation of AC-interval and PQ-interval. A strong correlation was found between AC-interval and PQ-interval in the present study.\(^2,4,9,17,18\) This correlation
Quantification of atrial contribution to diastolic filling

represents atrial electrico-mechanical coupling. However, in a subset of 11 of 34 (32%) patients AC-interval and PQ-interval differed. This may partly be related to the low heart rates of our patients. In 32 percent of the patients heart rate was < 60 beats per minute. With lowering heart rates, the diastasis period may become longer.\(^1\) The accuracy of the measurement of the diastasis point in the flow-volume loop may then decrease. The difference between AC-interval and PQ interval may also result from the correction we made for electrico-mechanical delay of ventricular activation. The electrico-mechanical delay of atrial activation does not need to be exactly the same. However, in respect of the exact match of PQ-interval and AC-interval in the majority of the performed studies this explanation is rather unlikely.

In all patients in which AC-interval and PQ-interval differed, the former always exceeded the latter, but never vice versa. In other words, the onset of an earlier atrial-ventricular flow can sometimes be detected before the beginning of electrical atrial activity. This passive diastasis flow has been described before and can be expected to occur in patients with low heart rates, increased ventricular stiffness, and increased ventricular relaxation rate.\(^6,19,20,21,22\) It may therefore be assumed that the AC-interval within the flow-volume loop represents the beginning of a combination of diastasis flow and atrial contraction flow. The PQ-interval on the electrocardiogram can be considered a better parameter of atrial contraction time than AC-interval.

Although it is conceivable to define the atrial contraction flow as beginning after atrial electrical activity, the measured flow in late diastole may remain a composition of passive diastasis flow and atrial contraction flow. One must therefore be cautious to define atrial contractile function on the basis of late diastolic flow only. This drawback is shared by other radionuclide angiography derived parameters on late diastolic filling such as peak late filling rate.

Limitations. There are two potential limitations to the present study. First, the methodological limitations of radionuclide angiography should not be underestimated. The assessment of global left ventricular filling requires a high temporal resolution and small cycle length fluctuations. Secondly, in this study different patient groups were included, which may impose on the accuracy of the assessment of diastolic filling patterns. However, no differences between these parameters were found between the various subgroups.

Conclusions. A close correlation was observed between the PQ-interval on the electrocardiogram and the atrial contraction time (AC-interval), a derivative of the shape of the left ventricular time-activity curve. In addition, a very close correlation was present between the subsequently calculated relative contributions of late diastolic filling to total diastolic filling. In patients with low heart rates however, the probability of AC-interval exceeding PQ-interval increased. This is likely due to a relatively small diastasis flow. It appears therefore better to use only the PQ-interval on the electrocardiogram, after
correction for electrico-mechanical delay, to define the beginning of atrial contraction rather than the AC-interval.

ACKNOWLEDGMENTS
We wish to thank Oebele Dijkstra and Henk Louwes for their technical assistance with the image analysis.

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