Optimization of the Arterial Input Function for Myocardial Perfusion Cardiovascular Magnetic Resonance

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Purpose: To determine how injection rate, cardiac function, and breathhold influence the arterial input function (AIF), in order to optimize the AIF in the clinical setting for quantitative myocardial perfusion cardiovascular magnetic resonance (CMR).

Materials and Methods: Gd (0.1 mmol/kg) bolus was injected at 3, 5, or 7 mL/second in 35 patients. In each cardiac cycle during the first-pass, a series of saturation recovery (SR) fast low-angle shot (FLASH) low resolution images with exponentially increasing SR delay times were acquired. Signal intensity (SI) time measurements were made from a region of interest (ROI) drawn in the ascending aorta (AA). The calculation of short T1s and thus peak Gd concentration \([\text{Gd}]\) was performed by fitting the mean ROI SI against SR delay times.

Results: The mean peak \([\text{Gd}]\) in the AA increased as injection rate increased from 3 mL/second (5.0 mM), to 5 mL/second (7.1 mM), to 7 mL/second (4 mM) \((P < 0.0001)\). The peak \([\text{Gd}]\) increased as the left ventricular stroke volume (LV SV) increased \((P = 0.01)\). Breath holding was not found to influence peak \([\text{Gd}]\).

Conclusion: In this study, we found that a high injection rate has advantages over lower injection speeds, although the duration of the AIF was apparently not significantly shortened by faster injection. The choice of expiration or inspiration as breathhold did not have a significant influence upon the AIF. Poor cardiac function was associated with a lower peak \([\text{Gd}]\), indicating that first pass perfusion measurements in these patients will be suboptimal.

Key Words: perfusion; cardiovascular magnetic resonance; arterial input function; contrast agent; T1 measurement


Materials and Methods

The study was approved by the local ethics committee (rest only, no stress). Studies were performed on 35 patients on a 1.5 T scanner (Siemens Sonata, Erlangen, Germany) using a four-element (two anterior, two posterior) phased-array coil. In 29 patients, the Gd-DTPA (Magnevist, Schering) boluses were given at rates of 3, 5, and 7 mL/second by power injection (Medrad, Spectris) in 10, 10, and 9 patients, respectively, chosen in...
random order, during end-expiratory breathhold. In six patients, the Gd bolus was given at 5 mL/second with the patient’s breath held in end-inspiration for comparative breathhold study. Each Gd bolus (0.1 mmol/kg) was immediately followed by a 10 mL normal saline flush, injected at the same rate as the Gd, to ensure complete delivery of the Gd. Each bolus was given via an 18-G cannula in the right antecubital fossa. For 45 cardiac cycles immediately following the delivery of the Gd bolus, a series of saturation recovery (SR) fast low-angle shot (FLASH) low resolution images (TE 0.35 msec, TR 1.06 msec, flip angle 5°, matrix 64 × 48, field of view (FOV) 40 × 40 cm) with exponentially increasing SR delay times were acquired in each cardiac cycle, starting immediately after the R wave. Six or seven images were acquired per cardiac cycle (i.e., SR delay times of 5, 10, 20, 40, 80, and 160 msec for the six images). The sequence used a 5° flip angle and a non-selective saturation prepulse to avoid fresh inflow effects. The short 50 msec FLASH sequence and a centric-out phase-encoding order enabled acquisition with short SR delays. A transverse plane through the ascending aorta (AA), as opposed to a short axis view of the left ventricular (LV) cavity, was selected for imaging to avoid cardiac motion effects. Potential signal dropout caused by T2* at peak [Gd] was eliminated by running some tests with saturation switched off (13).

The images were analyzed using in-house developed software (CMRtools, Cardiovascular Imaging Solutions, London, UK). A region of interest (ROI) was drawn in the AA, from which signal intensity (SI) measurements were made. From these measurements, the T1 in the AA each cardiac cycle during the first-pass of the Gd bolus was calculated, using the Levenberg-Marquardt fitting algorithm, which was adopted for a better exponential recovery fitting. From the T1 measurements, the shortest T1 of the first-pass and the peak [Gd] was calculated. The relationship of the blood T1 and [Gd] during first-pass can be expressed as follows:

\[
1/T_{1\text{Gd}} = 1/T_{10} + R_{\text{Gd}}[\text{Gd}] 
\]

where \(T_{1\text{Gd}}\) is the blood T1 in the presence of Gd and \(T_{10}\) is the normal blood T1 before the injection, which is usually 1200 msec. \(R_{\text{Gd}}\) is the relaxivity of the Gd (which is approximately 4.5 s–1mM–1) and [Gd] is the concentration of Gd. In blood the hematocrit is about 50% and Gd-DTPA does not enter this volume. However, the rapid rate of “proton exchange” between plasma and red blood cells (RBCs) ensures the magnetization equilibrium between these two fractions of the total blood (14).

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>3 mL/second</th>
<th>5 mL/second</th>
<th>7 mL/second</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV SV</td>
<td>78 ± 38</td>
<td>97 ± 36</td>
<td>87 ± 23</td>
<td>0.58</td>
</tr>
<tr>
<td>LV EF</td>
<td>55 ± 20</td>
<td>61 ± 14</td>
<td>55 ± 13</td>
<td>0.71</td>
</tr>
<tr>
<td>RV EF</td>
<td>47 ± 10</td>
<td>55 ± 11</td>
<td>52 ± 9</td>
<td>0.81</td>
</tr>
<tr>
<td>CO</td>
<td>5580 ± 2160</td>
<td>6660 ± 2940</td>
<td>5720 ± 1970</td>
<td>0.46</td>
</tr>
</tbody>
</table>

LV SV = left ventricular stroke volume (mL), LV EF = left ventricular ejection fraction (%), RV EF = right ventricular ejection fraction (%), CO = cardiac output (mL/minute).

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Expiration</th>
<th>Inspiration</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV SV</td>
<td>97 ± 36</td>
<td>80 ± 23</td>
<td>0.58</td>
</tr>
<tr>
<td>LV EF</td>
<td>61 ± 14</td>
<td>59 ± 20</td>
<td>0.71</td>
</tr>
<tr>
<td>RV EF</td>
<td>55 ± 11</td>
<td>48 ± 11</td>
<td>0.81</td>
</tr>
<tr>
<td>CO</td>
<td>6700 ± 2940</td>
<td>5220 ± 1267</td>
<td>0.46</td>
</tr>
</tbody>
</table>

LV SV = left ventricular stroke volume (mL), LV EF = left ventricular ejection fraction (%), RV EF = right ventricular ejection fraction (%), CO = cardiac output (mL/minute).
The duration of the AIF was used as a marker of the compactness of the AIF. The AIF duration was determined from the series of T1 measurements made. For each study, 50% of the SI value of the final SR image during the peak $[\text{Gd}]$ (shortest T1) cardiac cycle was set as the threshold. Then the cardiac cycles where the SI of a corresponding image crossed the threshold were marked. The duration of the AIF was calculated as the number of cardiac cycles between these two marks (rising and decreasing phases during the first-pass; Fig. 1).

In addition, left ventricular stroke volume (LV SV), left ventricular ejection fraction (LV EF), right ventricular ejection fraction (RV EF), and cardiac output were measured using a stack of short-axis cine balanced-SSFP images and the average RR-interval during the scanning in each patient.

For statistical analysis, analysis of variance (ANOVA) was used to test for difference between groups of parametric data (T1 and duration of AIF). Spearman’s rank correlation coefficient, Mann-Whitney U Test, and Kruskal Wallis were used to compare nonparametric groups. $P < 0.05$ was taken as statistically significant.

### RESULTS

The mean age of the study group was $51 \pm 16$ years and 29 were men. A total of 24 of the patients had known or suspected coronary artery disease, and the remaining patients had a known or suspected cardiomyopathy.

The mean LV EF was $57 \pm 16\%$. The wide range of T1 ($[\text{Gd}]$) values recorded from the patients was demonstrated in Fig. 2. There was no significant difference in cardiac function between the different injection rate groups (Tables 1 and 2).

### Injection Rate

The influence of injection rate on the AIF is summarized in Table 3. As the injection rate increased from 3 to 7 mL/second, the mean shortest T1 measured in the AA decreased from $44.1 \pm 14.1$ to $25.6 \pm 4.7$ msec ($P = 0.001$), and mean peak $[\text{Gd}]$ increased from $5.0 \pm 1.5$ to $8.4 \pm 1.4$ mM ($P = 0.002$). An increase in the injection rate from 3 to 5 mL/second reduced the mean shortest T1 from $44.1 \pm 14.1$ to $30.3 \pm 7.5$ msec ($P = 0.013$), and the peak $[\text{Gd}]$ increased from $5.0 \pm 1.5$ to $7.1 \pm 1.7$ mM ($P = 0.07$). An increase from 5 to 7 mL/second had no significant effect on AIF (Figs. 3 and 4). The spread of the shortest T1 values was lower as the injection rate increased (SD of the shortest T1 was $14.1$, 7.5, and 4.7, for 3, 5, and 7 mL/second injection rates, respectively), but was only statistically significant for the increase from 3 to 5 mL/second ($P = 0.014$). The mean AIF durations were $16.8 \pm 5.2$, $14.9 \pm 4$, and $12.8 \pm 7$ cardiac cycles for 3, 5, and 7 mL/second, respectively, but these decreases were not statistically significant (Fig. 5).

### Table 3

<table>
<thead>
<tr>
<th>Injection rate</th>
<th>3 mL/second</th>
<th>P</th>
<th>5 mL/second</th>
<th>P</th>
<th>7 mL/second</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortest T1 (msec)</td>
<td>$44.1 \pm 14.1$</td>
<td>0.013</td>
<td>$30.3 \pm 7.5$</td>
<td>0.56</td>
<td>$25.6 \pm 4.7$</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak (Gd) (mM)</td>
<td>$5.0 \pm 1.48$</td>
<td>0.07</td>
<td>$7.1 \pm 1.70$</td>
<td>0.47</td>
<td>$8.4 \pm 1.4$</td>
<td>0.002</td>
</tr>
<tr>
<td>AIF duration (cardiac cycles)</td>
<td>$16.8 \pm 5.2$</td>
<td>0.86</td>
<td>$14.9 \pm 4.0$</td>
<td>0.58</td>
<td>$12.8 \pm 7.0$</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*P values relate to comparison of data either side of the P value and overall ANOVA P values shown.
Cardiac Function

The shortest T1 values were significantly related to the LV SV, RV EF, and cardiac output ($P = 0.014$, $0.006$, and $0.039$, respectively), although not to the LV EF ($P = 0.18$) (Fig. 6). The relationship between the duration of the AIF and cardiac function parameters fell just short of statistical significance (Fig. 7).

Breathhold

No significant difference in the mean shortest T1 was found between the patients who held their breath at end-expiration, and those who held their breath in end-inspiration ($30.3 \pm 7.5$ and $35.2 \pm 16.1$, respectively).

No significant difference in the duration of the AIF was found between the patients who held their breath at end-expiration and those who held their breath in end-inspiration ($14.9 \pm 4.0$ and $14.5 \pm 8.6$ cardiac cycles, respectively; Fig. 8).

Figure 5. The change in AIF duration with different injection rates. There was no significant difference in AIF duration between the three groups.

Figure 6. Scattergrams of the shortest T1 measured in the AA against the left ventricular stroke volume (LV SV), right ventricular ejection fraction (RV EF), cardiac output, and left ventricular ejection fraction (LV EF). Linear regression lines are superimposed.
DISCUSSION

There is little data in the clinical setting examining the important influences upon the AIF. We have demonstrated that the rate of peripheral Gd injection influences the AIF. An increase in injection rate from 3 to 7 mL/second resulted in a significant increase in the peak [Gd] of the bolus reaching the left ventricle. The greatest part of this increase is found with the injection rate going from 3 to 5 mL/second, with a further smaller increase from 5 to 7 mL/second. Although there was a trend for the AIF to become more compact as the injection rate increased, the changes were not found to be statistically significant. An additional benefit from the injection rate increasing from 3 to 7 mL/second was that the spread between patients of the peak [Gd] was reduced. In other words, with the increase in injection rate, a compact, concentrated Gd bolus will be delivered more consistently.

The potential influence of different intrathoracic pressures associated with different breathhold techniques was not found to be significant in this study.

Cardiac function also had a significant effect upon the AIF. Decreasing cardiac function was associated with a decrease in the peak [Gd] of the bolus in the AA. However, cardiac function fell just short of statistical significance for influence upon the duration of the AIF.

All patient data were used in Figs. 6 and 7. Including all injection rates may only add “noise” to the correlation but not otherwise distort it, and was found to be necessary in view of the small number of patients at each injection rate.

One of the weaknesses of perfusion CMR is a lack of standardization of the technique. This work has developed and applied a technique for measuring dynamic short T1 values to investigate influences upon the AIF and thus help determine the optimal parameters for delivery of the Gd bolus. By optimizing the delivery of the AIF, the reproducibility and accuracy of quantitative perfusion may be improved. This technique for measuring short T1 values (15) can be used to investigate other potential influences upon the AIF, including site of injection, volume of normal saline flush, and type of Gd.

Some other factors such as flush rate were held constant in this study, please refer to Ref. 4 for a detailed analysis. A TE of 0.35 msec was used in this study.

**Figure 7.** Scattergrams of the AIF duration against the left ventricular stroke volume (LV SV), right ventricular ejection fraction (RV EF), cardiac output, and left ventricular ejection fraction (LV EF). Linear regression lines are superimposed.
which was shorter than the TE used in myocardial perfusion study. This short TE was only used for T1 estimation where the T2* effect is small. Longer TE may suffer T2* loses from high [Gd] in perfusion study, and there is the need for a separate specialized method for AIF measurement (13,16). It should be understood that this AIF study could not be acquired during a myocardial perfusion study, and also that only rest imaging was permissible.

In conclusion, we found the optimal injection rate was 7 mL/second. The majority of the benefit was found with injection rate increasing from 3 to 5 mL/second, with smaller additional benefit with the injection rate going from 5 to 7 mL/second. Choice of expiration or inspiration as breathhold was not found to have significant influence upon the quality of the AIF. Poor cardiac function was associated with an AIF of lower peak [Gd]. Further study is needed before we can obtain better understanding of where the bolus is diluted most, why the compactness of the bolus can not be altered by the injection speed, how injection speed influences a stress bolus, and other characteristics of the bolus.

REFERENCES