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# Automatic individual arterial input functions calculated from PCA outperform manual and population-averaged approaches for the pharmacokinetic modeling of DCE-MR images

## ABSTRACT

### Purpose

To introduce a segmentation method to calculate an automatic arterial input function (AIF) based on principal component analysis (PCA) of dynamic contrast enhanced MR (DCE-MR) imaging and compare it with individual manually-selected and population-averaged AIFs using calculated pharmacokinetic parameters.

### Materials and Methods

The study included 65 individuals with prostate examinations (27 tumors and 38 controls). Manual AIFs were individually extracted and also averaged to obtain a population AIF. Automatic AIFs were individually obtained by applying PCA to volumetric DCE-MR imaging data and finding the highest correlation of the PCs with a reference AIF. Variability was assessed using coefficients of variation and repeated measures tests. The different AIFs were used as inputs to the pharmacokinetic model and correlation coefficients, Bland-Altman plots and ANOVA tests were obtained to compare the results.

### Results

Automatic PCA-based AIFs were successfully extracted in all cases. The manual and PCA-based AIFs showed good correlation (r between pharmacokinetic parameters ranging from 0.74 to 0.95), with differences below the manual individual variability (RMSCV up to 27.3%). The population-averaged AIF showed larger differences (r from 0.30 to 0.61).

### Conclusion

The automatic PCA-based approach minimizes the variability associated to obtaining individual volume-based AIFs in DCE-MR studies of the prostate.



### Keywords

Perfusion, MRI, modeling, pharmacokinetics, automatic, variability

## INTRODUCTION

The pharmacokinetic modeling of dynamic contrast-enhanced magnetic resonance (DCE-MR) imaging is used to provide quantitative measurements of the microvascular perfusion properties of different tissues and biological situations, with a focus on the characterization of tumors and treatment response (1). To quantify the pharmacokinetic parameters, it is necessary to select a vascular function as input to the model, called the arterial input function (AIF). To incorporate this AIF data, several approaches have been proposed, such as reference experimentally derived AIFs (2,3), manual selection of individual AIFs (4,5), population-averaged AIFs (4-7) or automatically extracted personalized AIFs (8-11). Several of these studies have demonstrated that the quantitative parameters obtained from these models do not show significant differences based on how the AIF is selected (4-6). However, other studies report lower or very weak agreement (12,13).

This methodological variability hinders the process of standardizing a final methodology. However, there are also important efforts to provide reasonable degrees of standardization, such as the Quantitative Imaging Biomarkers Alliance (QIBA), an initiative of the Radiological Society of North America. In their DCE MR imaging Quantification Profile (14), they propose three alternatives to extract the AIF. The best recommendation about the calculation of the AIF is to use an automatically extracted AIF. As a second option, they recommend the manual selection, as described by Vonken et al. (15). However, this method has significant variability due mainly to flow artifacts. The last recommendation is about those situations where it is not possible to obtain an AIF because of anatomy, motion, flow artifacts or T2* effects. In these cases, population-averaged or reference AIFs could be used. However, an average AIF does not take into account the individual hemodynamics, thus losing the ability to characterize individual patients in a more accurate way. Also, with image processing and automatic volume-based approaches, the previous limitations can be overcome, at least partially.

The preferred methodology to decrease biases would allow the automatic extraction of the AIF without variability. With regard to this approach, several authors have proposed different solutions. Rijpkema et al. (8) proposal is based on the detection of early arrival of contrast media and thresholding the value of gadolinium concentration through an iterative

process; Singh et al. (9) used an approach based on thresholds with correction of partial volume effects; Shi et al. (10) proposed an iterative clustering algorithm called affinity propagation; Lin et al. (16) used a blind source separation algorithm to identify those voxels with the maximum arterial purity; and Kim et al. (11) developed an algorithm to select those voxels with similar contrast concentration homogeneity, allowing to select AIF voxels based on the well-known AIF profile and then correcting for partial volume effects. These methods vary in complexity, some of them being tested on very limited populations and thus, far from clinical validation. Also, they often concentrate on single slices, while it has been demonstrated that the choice of a certain slice has an important effect on the AIF selection and pharmacokinetic calculations (17).

In this context of automatically extracted personalized AIFs, we propose a simple method based on principal component analysis (PCA) to extract with minimum variability those voxels with a pure arterial behavior from a volumetric DCE-MR imaging data set of individual patients.

PCA (18) is a widespread statistical technique for the analysis of large data sets, which may have redundant information. This analysis allows a fast extraction of the sources of variation from large numbers of intensity vs. time curves, i.e. whole volumes analyzed on a voxel basis but taking all the data as a whole (19), hence taking profit of the correlation between pixels with the same behaviors. The output of PCA is a series of linearly uncorrelated latent variables called principal components (PC), which can be related to the expected dynamic behaviors of blood flow in organs and tissues; such as those used as schemes to categorize enhancement curves in types, i.e. 3-time-point method (20). When applying PCA to a whole volume of DCE-MR images, it can be demonstrated that the three largest sources of variation are usually associated to the arteries, normal enhancing organs and highly arterialized areas (19). The order of importance may change, depending on the relative contribution of these components to the whole volume of data.

We hypothesize that the combination of PCA and a priori knowledge of a typical AIF behavior can be used to segment voxels from which to compute individual AIFs without user intervention. The aim of this work is to introduce this methodology in a clinically relevant setting and compare it with manual individual selection and population-averaged AIFs, paying detailed attention to user dependent sources of variability.

## MATERIALS AND METHODS

### Patients

Sixty-five patients (age 62 ± 9 years old, mean ± standard deviation) who underwent routine DCE-MR examinations of the prostate were retrospectively included in the study. Among them, 27 patients had pathological confirmation of prostate carcinoma while 38 had negative biopsy with 6 months follow up without lesions. All the 65 cases were used for AIF calculations and comparisons.

In order to assess the performance of each AIF determination method to separate tumor from healthy tissue, a subgroup of 20 patients was defined. They were classified into healthy (10) and tumor (10). The criteria for the healthy group were negative biopsy, absence of family history of prostate cancer and stable PSA below 2.5 ng/ml (in at least two controls). The criteria for the tumor group were positive biopsy, PSA higher than 10 ng/ml, Gleason score higher than 7 and clinical status higher than T2a. For simplicity, only patients with tumor reliably located in the peripheral gland were included in this subgroup.

All patients gave written consent for the inclusion of their anonymized data in the study. Approval from the Ethics Review Board was obtained for this study.

### Image acquisition

The MR perfusion images were acquired in a 3 Tesla system (Philips Healthcare, Best, The Netherlands) with an 8-channel receiving surface coil and a 3D T1-weighted spoiled gradient echo sequence with the following parameters: TR / TE / FA = 3.4 ms / 1.7 ms / 40º, full prostate coverage (12 slices), matrix size = 192 x 192, reconstructed voxel size = 2 mm x 2 mm x 4 mm, temporal resolution of 3.4 s per dynamic, 80 dynamics (non-equally spaced), total acquisition time of 5 min, contrast agent Gd-DOTA (Dotarem®, Guerbet, France) and contrast dose 0.2 ml/kg followed by 40 ml of saline flush at 4 ml/s, using a power injector.

Also, a specific gradient echo with multiple flip angle sequence was acquired to obtain voxel-wise prostate T1 mapping calculations for the conversion of intensity values into contrast concentration measurements. The same geometry and characteristics as in the DCE

sequence were used, except for TR / TE / FAs = 3 ms / 2 ms / (2º, 7º, 10º, 20º, 30º, 40º, 50º). The multitransmit technology was used in order to obtain B1 mapping and minimize flip angle variations.

Finally, T2-weighted images were used to characterize prostate morphology and locate suspicious hypointense areas, with the following: 2D turbo spin echo sequence, ETL = 17, TR / TE / FA = 3858 ms / 90 ms / 90º and voxel size: 0.5 mm x 0.5 mm x 2 mm.

**Image analysis**

Selection of the AIFs

*Individual manual selection and variability assessment*

For every case, a radiologist (RP, 8 years of experience), manually drew a ROI on the right external iliac artery of the central slice. The AIF was obtained after averaging this ROI at each time point.

The variability was obtained by repeating the measures with a separation of one week and calculating the differences between the pharmacokinetic parameters using manually selected AIFs in 10 random cases, Four sources of variability were considered.

1. Selection of the AIF at the same location. The same radiologist selected the AIF at the right external iliac artery on the central slice after one week.
2. Different location within the same slice. A random AIF was selected at the central slice, either choosing the right/left internal/external iliac arteries.
3. Multiple manual ROIs per patient to obtain the individual AIF. To do this, the user drew 3 different ROIs instead of only one, again in the central slice and for a given artery (i.e. right external). Then these ROIs were averaged among themselves at each time point to calculate the individual AIF. To avoid influencing consecutive selections, the ROIs were not visible anymore once they had been selected.
4. Selection of the AIF from the same artery at different slices. The AIF was extracted from the same artery (i.e. right external), first in the 3rd and then in the 9th slice (cranio-caudal orientation).

*Population-averaged AIF*

To obtain the population-averaged AIF, all the individual AIFs selected at the right external iliac artery of the central slice were adjusted to correct for differences in onset times, ensuring that the peaks were matched in time before averaging the curves.

*Automatic PCA-based AIF*

PCA (18) is an orthogonal linear mathematical transformation that generates a new coordinate system from a data set, so that the coordinates of the new system (PCs) model the variance of the data in decreasing order, ensuring that all PCs are linearly uncorrelated.

In this study, PCA was applied to all the signal intensity curves of the DCE-MR volume. To do this, the original DCE-MR data were re-organized as a 2-dimension matrix X = (r x t), where r corresponds to the total number of observations (i.e. voxels) and t to variables (time steps). In this study, the matrix X had a size of 368640 (192x192x10) rows (observations) and 47 columns (t = 47). Notice that the extreme slices were excluded from the analysis as they can contain 3D spoiled gradient echo artifacts (this is demonstrated and discussed later on).

Mathematically, PCA solves this matrix system:

$$X = T \cdot P' + E$$

where X are the observations; T are the scores, which is the representation of X in the PC coordinate system; P' are the coefficients (also known as loadings) of each PC; and E is a residual matrix. Quantitatively, the PCs are iteratively obtained by maximizing the variance, obtained as

$$PC_i' \cdot S \cdot PC_i$$

where S is the covariance matrix of X.

Once the model is built, the interpretation of the PC's loadings allows identifying those uptake curves (i.e. voxels) that follow a certain pattern determined by the contribution of this pattern to the whole variance of the DCE-MR data set. The advantage of the AIF is that arterial blood follows a pattern quite distinct from the rest of uptake curves, so the voxels that have a strong correlation with the arterial-like PC (first pass with a fast upslope and fast washout) can be identified and located easily by looking for high scores in the corresponding PC.

In practice, although the arterial-like PC models a significant variance of the data set, a priori it cannot be known which PC it will correspond to, as PCA releases the components according to decreasing variance. This final order depends on each particular case. However, in our experience, the PC corresponding to the arterial-like behavior was always obtained within the three initial PCs.

To detect which PC corresponded to the AIF, the population-averaged AIF obtained in this study was used as reference. Other type of synthetic or experimentally derived (3) AIF-like curves could also be used, as it was just necessary to include a valid AIF shape as a priori knowledge. The PCs were correlated with this AIF-like curve, and the PC releasing the highest correlation was selected as the arterial PC. Before calculating the correlation, the PCs and the reference AIF were automatically adjusted by matching the maximum values in time.

Once the PC corresponding to the AIF was found, the voxels containing the purest contribution of this PC were located by unwrapping the 2D matrix X. The purest voxels were defined as those whose total signal contribution contained at least 95% of the selected PC, computed as the variance contribution of the selected PC to the whole signal intensity of the voxel. This threshold was robust enough to ensure that only pure arterial voxels were selected (i.e. they were all part of the iliac arteries), minimizing partial volume artifacts. Finally, the intensities of these voxels were averaged at each time point to obtain the AIF. By handling all the temporal information together, PCA allows extracting robust estimates of the AIF, taking into account the whole volume and therefore minimizing possible blood flow effects and ROI selection bias.

Although no human interaction was needed to extract the PCA-based AIF, two sources of variability were also assessed: the percentage threshold of the arterial-like PC contribution to the AIF (50%, 60%, 70%, 80%, 90% and 95%) and the effect of choosing a different number of slices rather than the whole volume for the PCA analysis (4, 8 and 10 central slices).

Prostate segmentation

In all cases, the same radiologist (RP, 8 years of experience) manually segmented the prostate by peripherally drawing ROIs in the slices in which it was visible. Afterwards,

voxel-by-voxel enhancement curves were automatically extracted to perform a voxel-based pharmacokinetic analysis.

Furthermore, manually selected ROIs were placed on the peripheral prostate glands of the subgroup of patients classified as healthy and tumor. For the healthy group, a representative sample of the peripheral gland was selected. For the tumor group, ROIs were carefully placed in the T2-weighted low signal intensity areas, corresponding to the region of positive biopsy location. The anatomic division of the prostate into sextants (left or right base, mid-gland or apex of the peripheral gland) was used as reference.

Pharmacokinetic modeling

The one-input two-compartment extended Tofts model was used (21), obtaining the pharmacokinetic parameters $K^{trans}$ (transfer constant), $k_{ep}$ (washout constant),$v_p$ (vascular space fraction) and $v_e$ (interstitial space fraction).

The concentration-time curves were obtained from the intensity-time curves by calculating the T1 variations with respect to pre-contrast T1 values after the injection of the contrast agent (22,23).

All image-processing methods were implemented in Matlab R2012a (The Mathworks Inc., USA).

**Statistical analysis**

In order to simplify the analysis and the results, for each patient a unique value of each pharmacokinetic parameter was handled, obtained by averaging the values of all the prostate voxels.

To assess the variability associated to the selection of the manual individual AIFs, the root mean square coefficient of variation (RMSCV) and the ANOVA test of repeated measures were used for each of the four variability experiments.

$$RMSCV = \sqrt{\frac{\sum_{i=1}^{N} \left( \frac{s_i}{\bar{x}_i} \right)^2}{N}}$$

where N is the number of repeated measures (N=10), $s_i$ is the standard deviation and $\bar{x}_i$ is the mean of each pair of measures. The RMSCV was used to assess the variability ranges

(low values meaning low variability), while the ANOVA looked for statistical significance in the differences. The same methods were used to assess the variability associated to the selection of the PCA-based AIF.

To compare the manual, population-averaged, and PCA-based AIFs, the relationships among the different sets of pharmacokinetic parameters were obtained using the Pearson's correlation coefficient and Bland-Altman plots. Case by case differences in absolute values were also assessed using ANOVA tests. A Student's t-test was performed to analyze the differences between healthy and cancerous tissues.

A p-value $< 0.05$ was considered statistically significant. When necessary, logarithmic data transformations were applied to ensure that data distributions were normal before applying the ANOVA tests. All statistical analyses were done in SPSS 19 (IBM, USA).

## RESULTS

### Manual AIF variability assessment

Table 1 reports the RMSCV of each parameter for the analysis of the variability associated to the manual individual selection of the AIF. Selecting and averaging multiple manual ROIs to obtain the AIF for a single patient showed the minimum variability for all the parameters (RMSCV from 1.9% to 2.9%), followed by the selection of the AIF at the same location (RMSCV from 9.6 to 15.2%). Finally, the variability associated to selecting different locations (i.e. arteries) within the same slice or to using the same artery at different slices was comparable, with different results depending on the pharmacokinetic parameter, but always higher than in the previous approaches (RMSCV from 13.6% to 25.3% and from 11.3% to 27.3%, respectively).

### Population-averaged AIF

The population-averaged AIF is shown in figure 1, along with the 95 and 5 percentiles of the 65 individual AIFs. The relative peak differences between the individual manually selected and the average AIFs were 38±62% (mean ± standard deviation, absolute values).

### PCA-based AIF

In all cases the PC associated to the AIF was obtained within the first three PCs. Figure 2 shows an example with several PCs extracted after applying PCA to a whole volume of DCE-MR images and the corresponding AIF (for visualization purposes only the first three PCs are shown). It can be seen that in this example the third component is already modeling noise. Then, the PC containing the AIF behavior was successfully selected in all cases as the PC maximizing the correlation with the average AIF, the DCE-MR volume was thresholded and a 3D arterial tree was obtained to extract the AIF (figure 3).

The choice of different percentages (50%, 60%, 70%, 80%, 90% and 95%) to threshold the AIF mask showed RMSCV of 10.1% for $K^{trans}$, 3.4% for $k_{ep}$, 7.6% for $v_e$ and 13.3% for $v_p$, with the ANOVA repeated measures test showing p-values of 0.215, 0.802, 0.534 and 0.314, respectively. When focusing on thresholds of 80% or higher, the RMSCV were 5.5%, 2.7%, 5.0% and 8.2%, respectively.

The choice of a different number of slices to perform the PCA (4 central slices, 8 central slices, 10 central slices and whole volume) showed RMSCV of 47.9% for $K^{trans}$, 20.9% for $k_{ep}$, 16.1% for $v_e$ and 13.7% for $v_p$, with the ANOVA repeated measures test showing p-values of 0.044, 0.213, 0.382 and 0.223, respectively. When the extreme slices were excluded from the analysis, the RMSCV fell drastically to 3.8% for $K^{trans}$, 5.4% for $k_{ep}$, 4.1% for $v_e$ and 5.7% for $v_p$.

The full process of applying PCA to the whole DCE-MR volume and finding the AIF took 2.6±0.3 seconds (mean ± standard deviation), using a computer with an Intel® Core™ i7 @3.60 GHz and 32 GB of RAM memory, without parallel computing.

Global comparison between the 3 AIFs

Table 2 shows the Pearson's correlations between the pharmacokinetic parameters obtained from each pair of AIFs. The highest correlations were found between the manual and the PCA-based AIFs, as they are both extracted from the same individual. The variations were caused by small differences in the height of the AIF peaks. On the other hand, the average AIF showed more disparities, both when compared to the manual and the PCA-based AIFs. Notice that $v_e$ was the parameter with the highest correlation among the three AIFs.

After calculating the case-by-case differences (table 3), the individual AIFs (manual and automatic PCA-based) showed the lowest discrepancy in all the parameters, followed by

the differences between the average and PCA-based AIFs. Last, the largest differences were seen between the manual and the average AIFs. There were statistically significant differences between the manual and the average AIFs ($p<0.001$), and between the average and the PCA AIFs ($p<0.001$) for all the parameters, whereas no significant differences appeared between the manual and the PCA methods.

When the differences in the AIF maximum (peak) values were analyzed together with the differences in the pharmacokinetic parameters on the same case-by-case basis, it was seen that the choice of the AIF had a direct effect on the pharmacokinetic parameters, especially when comparing the results of the average AIF with the other two AIFs (as figure 4 shows for $K^{trans}$).

Finally, the Bland-Altman plots (figure 5) showed a bias towards increasing differences between the resulting parameters as their estimated value increased (i.e. higher parametric values release larger differences between the different methods). This bias was more obvious when comparing the average AIF with the manual and PCA approaches, while it remained more constrained when comparing the manual and PCA AIFs.

Diagnostic performance of the three AIFs

Table 4 shows the pharmacokinetic parameters for each group of patients (healthy and tumor) using each AIF. $k_{ep}$ and $K^{trans}$ were the best parameters to separate between healthy and tumor tissue in the peripheral gland, showing statistically significant differences for the three AIFs (p-values ranging from 0.007 to 0.035). Qualitatively, $k_{ep}$ showed a slightly better performance to separate healthy from tumor areas. $K^{trans}$ showed similar values in the healthy patients for the three AIFs, while it showed quite lower values for the tumor area when using the average AIF. On the contrary, $k_{ep}$ showed lower values for the healthy area when using the manual AIF, while the values in the tumor were similar for the three AIFs. Figure 6 shows the parametric maps of $K^{trans}$ for one patient of each group, where the average AIF releases lower (tumor patient, 46% lower in comparison to the mean of the individual AIFs) or higher (healthy patient, 29% higher in comparison to the individual AIFs) values in comparison to the individual AIFs.

## DISCUSSION

In this work, an automatic method is proposed to extract the AIF from a whole volume of DCE-MR images, taking into account a priori shape information from a population-averaged AIF. The method is based on the application of PCA to the DCE-MR imaging data and the maximization of the correlation between each PC and the expected AIF behavior. Then the DCE-MR perfusion volume is thresholded ensuring that the segmented voxels have a very high contribution of the PC with the maximum correlation. Finally these voxels are averaged at each time point to release the individual PCA-based AIF. The method was tested on a relevant number of clinical studies, being robust and showing very low variability for all the cases.

The reproducibility of the pharmacokinetic parameters obtained from DCE-MR images has been an issue for a long time, as the choice of the AIF is an important source of variability (24-26). In this work, we have shown that the variabilities associated to the manual selection of an AIF are not negligible.

We have demonstrated that extracting an individual AIF by manually selecting and averaging several ROIs at the same locations showed the minimum variability. However, this method is more time consuming, and it does not prevent the differences obtained by selecting the AIF at different locations of the 3D data set (i.e. other arteries at the same slice or at different slices). Therefore, the lack of a validated protocol for the AIF manual selection when multiple choices are available poses difficult reproducibility issues. This enforces the need to consider whole volume automatic approaches to extract more accurate AIFs.

The use of population-averaged AIFs has been proposed for those situations where it is not possible to obtain a proper AIF, due to the area under analysis or to image acquisition limitations (4). Several studies show that there are not important differences in comparison with the individual AIF (4-7,27), while other studies report weaker agreement between the results of the average and the individual AIFs (12), especially with important differences in $K^{trans}$ (13). In our study, we found that both approaches cannot be taken as equivalent, as the analysis of the case-by-case differences shows. On the other hand, we also found that after performing an ANOVA among the global results corresponding to each AIF, using the

original values instead of the differences (results not shown in the study), they were not statistically different. This shows that on a population-level analysis the results are equivalent, but not on an individual basis.

The automatic PCA-based method was fast and robust and it showed very low variability to extract the AIF in all cases. The differences in the pharmacokinetic parameters compared to the manual individual AIF were below the range of manual selection variability. This suggests that the proposed approach can be used to obtain the AIF from a whole set of DCE-MR images without manual interaction and with accurate results, considering the expert manual selection as a ground truth. In this work, a 95% threshold was empirically set to obtain "pure" arterial behaviors, ensuring that it was highly selective with the voxels that were to be included as AIF. The effect of choosing a different threshold was also studied, demonstrating that there is also a relatively high variability when a lower threshold (~50%) is applied. The recommendation should be to set this threshold as high as possible (i.e. 90-95%) to ensure a fully arterial behavior in the AIF. Notice also that as it was a volume-based approach, the amount of candidate voxels was large enough to establish such high thresholds, so even if some arterial voxels were excluded from the selection, the sample was still sufficient to provide a robust AIF.

Another source of bias for the calculation of the automatic PCA was the inclusion of the extreme slices in the analysis. In 3D spoiled gradient echo sequences, these slices can have artifacts due to aliasing or to an incorrect excitation profile, so they can introduce errors when PCA is performed on the whole volume. When they were excluded the variability decreased drastically.

The diagnostic performance of each AIF was also studied by comparing the pharmacokinetic parameters of healthy tissue and tumors in the peripheral gland. In average, the three AIFs showed similar results, with relatively small differences and with $K^{trans}$ and $k_{ep}$ as the best parameters to separate both tissues. Again, we hypothesized that two facts probably occur here. Regarding the range of values, although on a case-by-case scenario there are differences, the population analysis masks them, showing homogenized populations. Regarding the statistical separability between healthy tissue and tumor, the choice of one AIF or another probably introduces a scaling effect in the pharmacokinetic parameters (especially $K^{trans}$), so that the relative differences between tissues are

nonetheless maintained. Therefore, as long as the AIF shape is preserved, this may not make a big difference for classifying tissues on an individual case. However, the lack of absolute individual measurements has limitations in order to obtain reference values.

Our $K^{trans}$ values for the healthy tissue were in the range of those released by Chen et al. (28) for the peripheral zone (0.23±11 $min^{-1}$). However, our values were quite higher for the tumor (0.57±0.18 $min^{-1}$ in Chen et al.), and more in the range of the study by Vos et al. (29), focused only in the tumor (0.63 to 1.44 $min^{-1}$, including low, intermediate and high-aggressive tumors). Comparisons with other works are difficult, as they do not normally distinguish between peripheral and central prostate glands.

Our study had several limitations. First, the PCA-based approach does not provide an organ-specific AIF, but the optimal AIF within the volume of DCE-MR images. In fact, more specific AIFs would require organ-specific reference AIFs, but probably with more variability associated to manual segmentation, due to spatial resolution restrictions. The selection of sub-volumes containing the arteries of interest could also help in obtaining more specific AIFs. A second limitation is the necessity to incorporate a priori knowledge of a standard AIF shape. However, as this type of shape is well known, it can be easily generated by mathematical models or incorporated as an empirical curve, such as in this work. Finally, the results of using analytical expressions for the AIF have not been explored (3,30-33). The comparison with these approaches was beyond the scope of this paper, considering that the MR studies had enough temporal resolution and a proper AIF could always be extracted from the volume of DCE-MR images.

In conclusion, an automatic PCA-based AIF was successfully obtained in all cases. The pharmacokinetic parameters obtained by the manual and PCA AIFs were comparable, with the PCA AIF showing differences below the range of the variability associated to the manual AIF selection. The population-averaged AIF showed significantly different results in comparison to the manual and the PCA-based AIFs. Taking the expert manual selection of AIFs as reference and considering its variability sources, the automatic PCA-based approach should be preferred, as it is a fast method with very low variability to extract individual AIFs for the pharmacokinetic modeling of DCE-MR studies.

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**TABLES**

**Table 1**. Manual AIF selection variability of the pharmacokinetic parameters obtained as the root mean square coefficient of variation (RMSCV) and the corresponding statistical significance of the ANOVA test with repeated measures. These values are obtained from repeating the manually selected AIF experiment in ten random cases, with a separation of one week between the analyses.

| | | AIF manual selection approach | | | |
|---|---|---|---|---|---|
| | | Same location | Different location in the same slice | 3 averaged ROIs at the same location | Same artery at different slices |
| $K^{trans}$ | RMSCV | 9.6% | 18.7% | 2.0% | 27.3% |
| | ANOVA's p-value | 0.043 | 0.202 | 0.076 | 0.002 |
| $k_{ep}$ | RMSCV | 9.7% | 13.6% | 2.8% | 11.3% |
| | ANOVA's p-value | 0.288 | 0.035 | 0.416 | 0.873 |
| $v_e$ | RMSCV | 15.2% | 25.3% | 2.9% | 24.7% |
| | ANOVA's p-value | 0.033 | 0.035 | 0.675 | 0.001 |
| $v_p$ | RMSCV | 14.4% | 23.7% | 1.9% | 14.5% |
| | ANOVA's p-value | 0.214 | 0.876 | 0.827 | 0.164 |

**Table 2**. Pearson's correlations (r) between the pharmacokinetic parameters obtained by each AIF estimation method with the statistical significance between brackets.

| | Manual vs. Average | Manual vs. PCA | Average vs. PCA |
|---|---|---|---|
| $K^{trans}$ | r=0.30 (p=0.015) | r=0.87 (p<0.001) | r=0.53 (p<0.001) |
| $k_{ep}$ | r=0.32 (p=0.009) | r=0.74 (p<0.001) | r=0.62 (p<0.001) |
| $v_e$ | r=0.61 (p<0.001) | r=0.95 (p<0.001) | r=0.64 (p<0.001) |
| $v_p$ | r=0.35 (p=0.004) | r=0.78 (p<0.001) | r=0.50 (p<0.001) |

**Table 3**. Results (mean and 95% confidence interval in brackets, in absolute values) showing the statistics of the case-by-case differences in the pharmacokinetic parameters between manual, average and PCA-based AIFs. The p-value represents the statistical significance of the comparisons between the groups of subtracted values.

| | (1) Manual-Average | (2) Manual-PCA | (3) Average-PCA | $p_{1-2}$ | $p_{1-3}$ | $p_{2-3}$ |
|---|---|---|---|---|---|---|
| $K^{trans}$ ($min^{-1}$) | 0.065 (0.049,0.086) | 0.022 (0.016,0.030) | 0.059 (0.044,0.079) | <0.001 | 0.665 | <0.001 |
| $k_{ep}$ ($min^{-1}$) | 0.206 (0.157,0.273) | 0.066 (0.050,0087) | 0.153 (0.117,0.202) | <0.001 | 0.135 | <0.001 |
| $v_e$ | 0.074 (0.055,0.101) | 0.025 (0.018,0.033) | 0.076 (0.056,0.103) | <0.001 | 0.934 | <0.001 |
| $v_p$ | 0.013 (0.010,0.017) | 0.004 (0.003,0.006) | 0.011 (0.001,0.015) | <0.001 | 0.489 | <0.001 |

**Table 4**. Results (mean and 95% confidence interval in brackets) showing the descriptive and ANOVA statistics of the pharmacokinetic parameters for each group of patients (healthy and tumor) using each AIF.

| | AIF type | Healthy | Tumor | p |
|---|---|---|---|---|
| $K^{trans}$ ($min^{-1}$) | Manual | 0.17 (0.08,0.26) | 0.97 (0.48,1.46) | 0.034* |
| | PCA-based | 0.18 (0.10,0.26) | 1.06 (0.52,1.61) | 0.033* |
| | Averaged | 0.16 (0.10,0.23) | 0.75 (0.39,1.12) | 0.035* |
| $k_{ep}$ ($min^{-1}$) | Manual | 0.44 (0.25,0.64) | 2.09 (1.43,2.76) | 0.007* |
| | PCA-based | 0.82 (0.22,1.43) | 2.20 (1.47,2.92) | 0.014* |
| | Averaged | 0.71 (0.19,1.24) | 2.14 (1.36,2.93) | 0.031* |
| $v_e$ | Manual | 0.35 (0.17,0.53) | 0.53 (0.35,0.71) | 0.173 |
| | PCA-based | 0.32 (0.11,0.54) | 0.54 (0.38,0.70) | 0.091 |
| | Averaged | 0.22 (0.12,0.32) | 0.41 (0.31,0.50) | 0.017* |
| $v_p$ | Manual | 0.01 (0.01,0.02) | 0.01 (0.00,0.02) | 0.358 |
| | PCA-based | 0.01 (0.01,0.02) | 0.01 (0.00,0.02) | 0.470 |
| | Averaged | 0.03 (0.00,0.06) | 0.04 (0.00,0.09) | 0.561 |

## FIGURE LEGENDS

**Figure 1**. Population-averaged AIF obtained at the external iliac arteries of the 65 patients. All curves were corrected for onset times before averaging. The continuous line shows the average and the dashed lines the 95- and 5-percentile.

**Figure 2**. Principal components (PCs) obtained from the PCA of all the DCE-MR images. First three PCs: PC1 corresponds to the typical behavior of an artery, PC2 represents a typical slow progressive enhancement and PC3 corresponds to noise. The order may vary according to the explained variance of each PC. In some cases, PC3 still models a physiologically relevant behavior.

**Figure 3**. Automatic volumetric segmentation of the purest arterial component based on the principal components analysis. (a) The segmented area corresponds to those voxels with the highest contribution of the arterial component (PC1 in figure 2), corresponding to the external iliac arteries. (b) The AIF is obtained by averaging the contributions of all voxels at each time point.

**Figure 4**. Case-by-case analysis of the differences in $K^{trans}$ originated by differences in the maximum (peaks) of the AIFs. a) Manual vs. average AIFs. b) Manual vs. PCA-based AIFs. c) Average vs. PCA-based AIFs. The points in b) are more clustered, reflecting smaller differences than when comparing with the average AIF.

**Figure 5.** Bland-Altman plots showing the mean and differences for $K^{trans}$. a) Manual vs. averaged AIFs. b) Manual vs. PCA-based AIFs. c) Averaged vs. PCA-based AIFs. Both a) and c) show that the differences with the averaged AIF increase when the mean value of $K^{trans}$ increases. The differences between the manual and the PCA-based AIF are more bounded.

**Figure 6**. Parametric colored map showing $K^{trans}$ overlapped on a T2-weighted image. Top row: a low signal intensity area can be seen on the left side of the peripheral gland related to the presence of a tumor (arrow). In this case, the average AIF was quite higher than the individual AIF of the patient, so the $K^{trans}$ values using the average AIF (a) were underestimated in comparison to those using the individual AIFs, being b) the manual AIF and c) the PCA-based AIF. For visualization purposes, the parametric maps show only $K^{trans}$ values higher than 0.2 $min^{-1}$. Bottom row: in this case the average AIF was lower,

releasing higher values for $K^{trans}$ (d) in comparison to the individual (e) and PCA-based (f) AIFs, which showed similar results.