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DESIGN AND EVALUATION OF AN ABBREVIATED PIXELWISE DYNAMIC CONTRAST ENHANCEMENT ANALYSIS PROTOCOL FOR EARLY EXTRACELLULAR VOLUME FRACTION ESTIMATION

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1 **DESIGN AND EVALUATION OF AN ABBREVIATED PIXELWISE**
2 **DYNAMIC CONTRAST ENHANCEMENT ANALYSIS PROTOCOL FOR**
3 **EARLY EXTRACELLULAR VOLUME FRACTION ESTIMATION**

1 **ABSTRACT:**

2 **Introduction**

3 T1-based method is considered as the gold standard for extracellular volume fraction
4 (ECV) mapping. This technique requires at least a 10 minutes delay after injection to
5 acquire the post injection T1 map. Quantitative analysis of Dynamic Contrast
6 Enhancement (DCE) images could lead to an earlier estimation of an ECV like
7 parameter (2 minutes). The purpose of this study was to design a quantitative pixel-
8 wise DCE analysis workflow to assess the feasibility of an early estimation of ECV.

9 **Methods**

10 Fourteen patients with mitral valve prolapse were included in this study. The MR
11 protocol, performed on a 3T MR scanner, included MOLLI sequences for T1 maps
12 acquisition and a standard SR-turboFlash sequence for dynamic acquisition. DCE
13 data were acquired for at least 120s. We implemented a full DCE analysis pipeline
14 with a pre-processing step using an innovative motion correction algorithm (RC-REG
15 algorithm) and a post-processing step using the extended Tofts Model (ECV_{ETM}).
16 Estimated ECV_{ETM} maps were compared to standard T1-based ECV maps (ECV_{T1})
17 with both a Pearson correlation analysis and a group-wise analysis.

18 **Results**

19 Image and map quality assessment showed systematic improvements using the
20 proposed workflow. Strong correlation was found between ECV_{ETM}, and ECV_{T1}
21 values (r -square=0.87).

22 **Conclusion**

23 A DCE analysis workflow based on RC-REG algorithm and ETM analysis can provide
24 good quality parametric maps. Therefore, it is possible to extract ECV values from a
25 2 minute-long DCE acquisition that are strongly correlated with ECV values from the
26 T1 based method.

27 **KEYWORDS:** Cardiac MR; DCE-MRI; REGISTRATION; PERMEABILITY; ECV

1 **Manuscript:**

2 **1 INTRODUCTION :**

3 Myocardial extracellular volume (ECV) is considered as a key biomarker for the
4 quantification of myocardial fibrosis using magnetic resonance imaging (MRI) [1], [2].
5 It was first qualitatively studied on local infarcted area with the so-called late
6 gadolinium enhancement or delayed enhancement technique [3], which is based on
7 the signal enhancement observed in the myocardium few minutes (15-20 minutes i.e.
8 at the equilibrium of concentrations between compartments) after the injection of a
9 paramagnetic contrast agent (CA) distributing within the extracellular extravascular
10 space (EES) [4]. The accumulation of contrast agent within large EES, such as in
11 infarcted tissues, leads to a brighter signal on T1-weighted (T1w) images than on the
12 healthy myocardium [5]. Quantitative assessment of ECV has been lately developed
13 using T1 measurements before injection and once the equilibrium state of CA
14 concentrations between vascular space and EES has been reached [6]. This
15 technique is well-known and denoted as ECV mapping. The very straightforward
16 formula and its ease of use (as long as specific cardiac T1 mapping sequences are
17 available) made it remarkably popular in the last few years and yield very promising
18 results for diffuse fibrosis diagnosis [1], [7]. However, the major disadvantage of this
19 technique lies in its duration, with a required long waiting time before reaching the
20 steady-state concentration between injection and acquisition of the post-injection T1
21 map (>10 minutes according to the latest statement of the SCMR community [8]).
22 Cardiac MRI (CMR) exams are among the longest MRI exams and there is a crucial
23 need to shorten the total duration of CMR exam. Several options have been
24 investigated in order to assess myocardial tissue pathophysiological state in a shorter
25 time. Non-contrast enhanced imaging with diffusion weighted imaging (DWI) has

1 been investigated for more than a decade [9]. However, despite its huge potential,
2 cardiac DWI is very complex to set up and improvements are still required before its
3 use in clinical routine with a high reproducibility[10]. Another avenue of research
4 consists in taking advantage of T1w Dynamic Contrast Enhanced (DCE) acquisition,
5 which could bring early and new insights on the myocardium viability. From the early
6 works of Wilke et al.[11] and Jerosch-Herold et al. [12] to the latest works of Knot et
7 al. [13] using fully automatic in-line perfusion analysis [14], myocardial perfusion
8 quantification has been mostly focusing on myocardial blood flow estimation from the
9 first-pass analysis of the CA injection. Several models have been explored to quantify
10 the myocardial blood flow; but constraint Fermi deconvolution [12] or Blood Tissue
11 Exchange Model [15] remain the most studied to this day. Bi-compartmental models
12 like the Extended Tofts Model (ETM) based on the Kety model have also been
13 investigated with various conclusions regarding the impact on myocardial viability
14 assessment [16]. Larsson et al.[17] showed that the extracellular extravascular
15 volume fraction V_e extracted from pharmacokinetic models could be a good
16 predictive factor of the interstitial volume, which is also quantified with the ECV
17 method. A little bit more than a decade ago, Pack et al. [18] investigated the
18 relationship between the compartmental parameter V_e and the so called “*steady-*
19 *state*” tissue enhancement method. They demonstrated a non-significant difference
20 between these two parameters. However, they could not compare their results to
21 ECV extracted from T1 maps largely validated against histology. More recently,
22 Kunze and colleagues compared measurements of ECV using the T1 maps method
23 (equilibrium ECV) with the ECV extracted from perfusion quantification (perfusion
24 ECV) [19]. They demonstrated a good correlation between ECV values extracted
25 from both methods. They used a hierarchical modeling approach to estimate ECV

1 from perfusion data using up to 5 parameter-models. This approach did not include
2 standard permeability model such the 3 parameter-ETM.

3 The present work aims to pursue these investigations by comparing ECV values
4 obtained from T1 maps (ECV_{T1}) with those derived from parameters of the ETM
5 analysis of perfusion imaging (ECV_{ETM}).

6 The first step in the development of a full DCE analysis pipeline was to implement a
7 motion correction algorithm for images acquired in free breathing. This step
8 presented a critical challenge due to the joint presence of contrast variation and
9 respiratory and cardiac motion . Our vendor-provided in-line motion correction
10 algorithm, MOCO [20], aligns each image of the series to the previous one. It is
11 known to be prone to registration error propagation and to eventually introduce
12 distortion in registered images, especially when acquisition time exceeds first-pass
13 (about 1min) [20]. Thus, myocardial first-pass DCE registration has been and is still
14 extensively investigated using various strategies such model-based registration [21],
15 independent component analysis [22] or using robust large displacement optical flow
16 [23]. This problem was already assessed in DCE studies on other organs. For
17 instance, Hamy et al. used a robust Principal Component Analysis to register DCE
18 data from bowel [24] employing a similarity indicator robust to intensity variation
19 called residual complexity (RC) [25]. We hypothesized that such similarity indicator
20 could also be a suitable solution to myocardial DCE registration.

21 Thereby, the goal of this study was two-fold. First, it aimed to assess our proposed
22 registration algorithm compared to the vendor's in-line registration algorithm MOCO.
23 Second, it aimed to investigate the feasibility of an early ECV estimation from 2min-

- 1 long DCE-MRI analyzed with the Extended Tofts Model compared to the regular
- 2 10min ECV estimation from the T1 mapping method.

1 2 MATERIALS AND METHODS:

2 2.1 Acquisition of DCE data and T1 maps

3 MR data of 14 patients, with suspected or diagnosed mitral valve prolapse were
4 extracted from the STAMP (STretch and Myocardial Characterization in
5 Arrhythmogenic Mitral Valve Prolapse) study (NCT02879825), and were analyzed for
6 the purpose of this study. STAMP was approved by the local committee of ethics,
7 wherein all participants provided written informed consent. Every patient had a single
8 measure of hematocrit (hct) that was used for ECV calculation. The CMR protocol
9 was performed on a 3Tesla (T) MR scanner (Prisma, Siemens Healthineers,
10 Erlangen, Germany).

11 Injection consisted in a 0.15mmol/kg bolus Gd-DOTA (Dotarem[®], Guerbet, France) at
12 least 6 seconds after the beginning of the dynamic acquisition at a rate of 4mL/s. The
13 pre-bolus T1 map (T1₀ map) was acquired with a single shot MOLLI set of 8 TI
14 samples (5(3)3) on 8 slices covering the heart from the left atrium to the mid
15 ventricular area (TR/TE: 283/1.12ms, matrix: 256x220, in plane resolution:
16 1.40x1.40mm², Slice Thickness: 8mm). DCE series lasted for at least 116 seconds in
17 free breathing or partial free-breathing using a SR-TurboFLASH sequence (TI: 95ms,
18 TR/TE: 116/0.97ms, flip angle:10°, matrix: 160x116, in plane resolution:
19 2.25x2.25mm², slice thickness: 8mm). The acquisition was cardiac gated meaning
20 temporal resolution varied (mean: 0.95±0.13s) depending on the patient's heart rate.
21 To ensure a temporal resolution equal to one RR-interval, the maximum number of
22 slices was defined by the acquisition time available within one RR interval. This
23 resulted in the acquisition of one to two slices maximum par RR interval. Post-T1
24 map was acquired with a single shot MOLLI sequence set of 9 TI samples for
25 4(1)3(1)2 at least 15 minutes after the injection T1₀ map, DCE series and post-

1 T1map slices were set to be automatically acquired at the same location with the
2 same orientation and extra care was taken to ensure the acquisitions were performed
3 during the same cardiac phases.

4 **2.2 ECV mapping using extended Tofts modelling**

5 The processing pipeline of this study (Figure 1) was implemented in Matlab® (The
6 Mathworks, Natick,MA, USA).

7 The first step consisted in the registration of the magnitude images of the DCE series
8 using our homemade registration algorithm (RC-REG). DCE acquisitions were
9 normalized using a pre-scan calibration in order to attenuate signal inhomogeneity
10 from the coil profile across the slice. The specific difficulty met with DCE images
11 registration is the contrast change from one image to another, especially during the
12 bolus arrival. The originality of this registration algorithm was the use of two reference
13 images for the successive registration of pre-bolus and post-bolus acquisitions.
14 Registration of DCE images was based on a 2-dimensional non-rigid algorithm using
15 b-spline deformation model with gradient descend optimization using the residual
16 complexity (RC) as similarity measure included in the Medical Image Registration
17 Toolbox developed by Myronenko et al. [25]. RC-REG algorithm is further described
18 in Figure 2.

19 The algorithm was set to iterate until both the mean and standard deviation (SD) of
20 the Structure Similarity (SSIM) [26] scores of the registered DCE series reached
21 empirically determined cutoff values (mean > 0.81 and std < 0.028). Thus, the
22 algorithm kept iterating using the newly registered DCE images as a starting point.
23 This allowed the algorithm to manage DCE series with large respiratory motion,
24 which leads to blurry averaged DCE series after the first iteration.

1 The T_{10} map was resized and downsampled to fit the DCE series resolution and
2 FoV. Then, T_{10} map was aligned to the registered DCE series averaged image using
3 the Matlab® multimodal 2-dimensional rigid registration algorithm (function
4 `imregister`). A pixel-wise signal to CA concentration conversion on the DCE series
5 was then performed.

6 To shorten post-processing, automatic cropping was applied to all DCE images. First,
7 the region of interest was selected based on both the maximum intensity of the DCE
8 series and shape segmentation of the Left Ventricle (LV) chamber. Then, the
9 coordinates of a rectangle were calculated to widen the region of interest area and to
10 prevent over cropping. The resulting cropping was applied to the corresponding T_{10}
11 map. Registration quality measurements were evaluated on this area of interest.

12 DCE signals were interpolated using a piecewise cubic Hermite interpolation
13 algorithm to a constant temporal resolution of 0.5s.

14 AIF was measured for each exam. Since it has been shown that RC algorithm does
15 not alter signal of the corrected image [24], [25], we considered that sampling the
16 AIF from the RC-REG series was the best solution to extract reliable signal intensity
17 dynamics of the vascular space without being polluted by motion. A manual region of
18 interest (ROI) was placed in the center of LV cavity to extract blood signal intensity
19 dynamics.

20 Pixel-wise dynamic T1 values were processed from (pixel-wise) normalized signal
21 intensity curves associated with baseline signal mean value, i.e. before injection
22 (acquired for at least 6 seconds), and corresponding T_{10} voxel value using the signal
23 equation of the SR-turboFLASH sequence. Ultimately, CA concentration was

1 calculated for each pixel using the linear relationship between T1 and CA
 2 concentration:

$$3 \quad \frac{1}{T1_{i,j,k}} = r \cdot [CA]_{i,j,k} + \frac{1}{T1_{0\ i,j}}, \quad (2)$$

4 with i,j the coordinates of the pixel of interest, k the time, T1_{i,j,k} the T1 value; r the
 5 relaxivity of the CA at 3T, 3.6 mM⁻¹.s⁻¹, [CA]_{i,j,k} the CA concentration and T1_{0 i,j} the T1
 6 extracted from T1₀map.

7 Extended Tofts modeling was achieved using a trust region least square algorithm
 8 generating K_{trans}, K_{ep} the flux rate parameters and V_b the blood volume fraction
 9 maps using the following formula:

$$10 \quad Ct(t) = Cb(t) * K_{trans} \cdot e^{-K_{ep} \cdot t} + Cb(t) \cdot Vb, \quad (3)$$

11 with Ct, the tissue concentration and Cb the blood concentration. Ve' maps were
 12 calculated using the relation Ve' = K_{trans}/K_{ep}. Before fitting, AIF was temporally
 13 shifted to adjust the bolus arrival time to the one of the dynamic tissue concentration
 14 curve Ct(t) by computing cross-correlation between the two curves. Extracellular
 15 extravascular volume fraction Ve was calculated by correcting Ve' with each subject's
 16 hematocrit (hct) so that: Ve = Ve' · (1-hct). Likewise, plasma volume fraction was
 17 computed such as Vp = Vb · (1-hct). ECV corresponds to the non-cellular volume
 18 fraction of a tissue[1], [27], and therefore to the EES plus the plasma volume fraction.
 19 We calculated the ECV values from ETM analysis so that ECV_{ETM} = Ve+Vp. ECV_{T1}
 20 were computed using the classical T1 maps technique and individual hct values [7].
 21 Native and post blood T1 were measured within a ROI manually drawn in the center
 22 of the LV cavity. Full size native and post T1 maps were registered with the same

1 multimodal 2D rigid registration algorithm used to register the $T1_0$ map and the mean
 2 DCE series. ECV maps were computed with the following formula:

$$3 \quad ECV_{T1(i,j)} = (1 - hct) \cdot \frac{(R1_{myo(i,j)}^{post} - R1_{myo(i,j)}^{native})}{(R1_{blood}^{post} - R1_{blood}^{native})},$$

4 where $R1_{myo/blood}^{post/native}$ correspond to post/native $1/T1$ of the myocardial/blood.

5 **2.3 Evaluation of the motion correction and permeability maps**

6 The registration algorithm was qualitatively assessed by extracting dynamic line
 7 profiles of DCE series. Two line-profiles were extracted for each DCE series. Line
 8 profiles from unregistered (UNREG), in-line MOCO algorithm (MOCO) and RC-REG
 9 series were compared. Registration quality of the proposed algorithm was also
 10 assessed on permeability maps, looking at the absence of abnormal deformation of
 11 the LV. Also, homogeneous and/or a less “noisy” map was considered of a global
 12 higher quality.

13 Permeability parameter measurement was achieved within ROI manually drawn
 14 around the endocardium and epicardium of the LV and divided into the regular AHA
 15 (American Heart Association) segments [28] on one to two slices per subject (from
 16 basal to medial level). Because slices were basal to medial, we concatenated
 17 segments from these slices into a single segment value to finally extract 6 segment
 18 values per subject. Permeability measurements were performed only when the
 19 thickness of the whole myocardium wall was sufficient to avoid any partial volume
 20 effect.

1 **2.4 Comparison between ECV_{ETM} and ECV_{T1}**

2 Diffuse fibrosis is a process at the root of several cardiomyopathies and is not
3 restricted to a specific location but that affects the whole myocardium. Therefore, we
4 considered the global myocardial mean value of ECV_{ETM} and ECV_{T1} as
5 representative of the general state of fibrosis infiltration. For each patient, we
6 therefore calculated the ECV median \pm median absolute deviation (mad) values from
7 the measured segments.

8 Pearson correlation with a significance level of 0.05 was used to compare ECV_{ETM}
9 from the three series and ECV_{T1} myocardial values for the three series: UNREG,
10 MOCO and RC-REG.

11 We chose to evaluate the discrimination power of ECV_{ETM} versus ECV_{T1} as follows:
12 an ECV_{T1} value higher than 0.30 was considered as abnormal, splitting the patients
13 into two groups. We then evaluated the difference between the two groups of ECV_{T1}
14 and associated ECV_{ETM} values with a permutation test.

1 **3 RESULTS:**

2 **3.1 Evaluation of the motion correction and permeability maps**

3 Line profiles inspection of the fourteen exams showed, except for a few exceptions
4 mentioned later, that respiratory motion correction was possible with MOCO and RC-
5 REG algorithms (i.e. respiratory patterns were smoothed). Figure 3 provides two
6 examples of typical line profiles with two different orientations obtained from UNREG,
7 MOCO and RC-REG series. One can observe that MOCO registration introduced
8 image distortions after the first-pass period on every exam, which never occurred
9 with the RC-REG algorithm. These registrations are available in supplementary
10 materials where the deformations of the LV on MOCO series can clearly be seen.

11 It has to be noted that DCE series from exam 11, which showed very large
12 respiratory movements, was neither properly registered by MOCO nor the RC-REG
13 algorithm.

14 Figure 4 shows two examples of ETM permeability maps. Visual assessment of
15 permeability maps indicates that maps computed from MOCO DCE series were also
16 highly impacted by the deformation generated during registration process. Maps
17 extracted from UNREG DCE series appeared to be affected at different levels by
18 respiratory motion, especially on inferior segments, which exhibited heterogeneous
19 values for each permeability parameter. RC-REG permeability maps showed more
20 homogeneous permeability parameter values over the left ventricle than permeability
21 maps with other registration techniques.

22 Two exams had to be discarded from the analysis because the myocardium
23 thickness (<2 pxls) did not allow an ROI to be placed without including voxels
24 affected by partial volume effect.

1 **3.2 Comparison between ECV_{ETM} and ECV_{T1}**

2 Figure 5 highlights the excellent correlation between ECV_{ETM} and ECV_{T1} values (r-
3 square=0.87) with a unity slope but a slight offset (= -0.05).

4 As shown in Figure 6, the 12 exams were split into two small groups of unequal size
5 (n=8 for ECV_{ETM}≤0.30 and n=4 for ECV_{ETM}> 0.30). For both ECV methods, permutation test
6 gave a statistically significant mean difference between the two groups. Boxplot
7 analysis indicated a clear differentiation between the two groups of ECV_{ETM} series
8 with no overlapping of the upper and lower whiskers (lower group ECV_{ETM}>0.30
9 corresponded to ECV_{ETM}=0.22; upper group ECV_{ETM}<0.30 corresponded to
10 ECV_{ETM}=0.20) which was naturally also the case for ECV_{T1} subgroups (lower group
11 ECV_{T1}>0.30 corresponded to 0.32; upper group ECV_{T1}<0.30 corresponded to 0.28)
12 which was our reference.

1 4 DISCUSSION:

2 4.1 Evaluation of the motion correction and permeability maps

3 In order to proceed to ECV_{ETM} evaluation, we first proposed a novel DCE imaging
4 registration algorithm. This algorithm used RC as a similarity indicator between two
5 images. Well known in the post-processing community [29], residual complexity has
6 been used in few MRI studies and mostly for abdominal exams [24], [30], [31]. It is
7 only very recently that Scannell et al. used RC as a similarity indicator integrated in a
8 Robust principal component analysis (RPCA) based registration algorithm for first
9 pass perfusion imaging [32]. Compared to the latter work, our algorithm is based on
10 an iterative optimization process of 2 similarity indicators (SSIM and RC), which could
11 improve the quality of the registration compared to a two-step registration process. In
12 this study, we also demonstrated the feasibility to register perfusion data from longer
13 acquisition than what was assessed previously. Furthermore, the impact of the
14 proposed registration algorithm was evaluated on both native DCE data and
15 permeability maps.

16 Results of our study confirmed that RC-based algorithms offer better registration for
17 free-breathing DCE cardiac MRI images than the vendor's in-line MOCO in terms of
18 line profiles (figure 3), and permeability maps quality (figure 4). MOCO is well known
19 to incrementally introduce distortions on the corrected images as the processed
20 image is further away from the bolus arrival in the LV. This phenomenon is well
21 described in literature [20], [33], [34] and can be observed in figure 3 and
22 supplementary videos.

23 RC-REG is a 2D registration algorithm (like MOCO), which implies that it is
24 intrinsically unable to register through-plane motion leading to lower similarity metric

1 scores from one image to another. It is also a post-processing algorithm and
2 therefore dependent on the quality of the ECG gating during the prospective image
3 acquisition. This acquisition technique is known to be sensitive to irregular heart rates
4 [35], [36] and even if DCE images were correctly aligned, the apparent thickness of
5 the left ventricle may vary if such mistriggered data are present. This issue was not
6 address in this work but it is visible on supplementary material 1. Such isolated
7 mistriggered acquisitions could be potentially discarded from the DCE dataset and
8 replaced using temporal interpolation with very low impact on the final analysis.
9 However, several consecutive acquisitions at wrong cardiac phases during the bolus
10 arrival might lead to strongly biased parameter estimation, which was not
11 encountered during this study. Despite these common limitations (shared between
12 MOCO and other registration algorithms) our solution demonstrated better results
13 both qualitatively and quantitatively compared to MOCO. It also showed comparable
14 results compared to other more complex algorithms proposed in the literature [23],
15 [32], [37].

16 Two exams were acquired in a partial free-breathing paradigm, i.e. the patient was
17 asked to hold his/her breath as long as possible [35]. The reference image for post-
18 injection data was found to be in a very different location from the reference image for
19 pre-injection data for these patients. Our registration technique did not fully overcome
20 this limitation resulting in a slight shift of the data particularly visible in the right
21 ventricle (figure 3.B). Nonetheless, it had no visible impact on the processed
22 permeability maps. It has to be noted that the registration between reference 1 (from
23 baseline series) and reference 2 (from entire series), resulting images would also be
24 inadequate in the case of poor cardiac triggering between the baseline acquisition
25 and the acquisition after the bolus arrival. The non-rigid nature of this deformation

1 would lead to incomplete registration of those two images and would end as being
2 discarded in the study. The use of a non-rigid registration for the alignment of these
3 two reference images would be an interesting avenue of research, although it would
4 not guarantee that the aligned pixels would coincide with a real volume alignment
5 because of the complex nature of cardiac fibers motion between cardiac phases.

6 Permeability maps from RC-REG series appeared to be less noisy and provided
7 more homogeneous ETM parameter values than MOCO and UNREG maps.
8 Distorted registration with MOCO yielded distorted ETM parameters maps as shown
9 in figure 4.

10 It is noteworthy that two exams had to be discarded from the segment analysis
11 because of a too thin left ventricle myocardial wall, which did not allow for the
12 extraction of a sufficient number of voxels not affected by partial volume effect. This
13 underlines the drawback of low-resolution acquisitions in first-pass protocols. This is
14 a common limitation to all quantitative perfusion methods and developments still have
15 to be made especially for application to patients with dilated cardiomyopathy.

16 In one case, $T1_0$ map and DCE slices were not acquired in the exact same locations.
17 This exam represents one limitation of our workflow, which requires the $T1_0$
18 information (DCE baseline) from a separate breath-held acquisition of $T1$ map.
19 Cernicanu and Axel method [38] for the signal to [CA] conversion could bring a good
20 solution to avoid the use of $T1$ mapping and its drawbacks. Another point of
21 improvement of our workflow would be to include a better way to measure or correct
22 the AIF which would guarantee a better signal to CA concentration conversion and
23 ultimately a more accurate measure of ETM parameters. There is still no consensus
24 on which method to use but dual bolus [39], [40] or dual sequence [14], [41] methods

1 are valuable, although imperfect candidates to ensure a more reliable AIF
2 measurement.

3 **4.2 Comparison between ECV_{ETM} and ECV_{T1}**

4 We found a very strong correlation between ETM and T1-based ECV average
5 myocardial values. ECV_{ETM} values exhibited lower absolute values compared to
6 ECV_{T1} . In their study, Kunze et al. [19] also reported both strong correlation between
7 perfusion and ECV_{T1} and lower values for ECV estimated from DCE data. This
8 underestimation was slightly more pronounced in our study. The use of ETM, which
9 is a suitable model only under certain conditions of perfusion and flow in the tissue
10 [42], could explain a sub-optimal estimation of ECV. Although, the presented results,
11 in line with the literature, illustrate the feasibility of ECV measurement using DCE-
12 MRI.

13 ECV_{ETM} values were able to separate the two groups as distinctly as ECV_{T1} values.
14 One might add that the cutoff ECV value was chosen from the reported values in the
15 literature to discriminate between healthy and pathologic subjects, but this arbitrary
16 separation requires a larger study to confirm its clinical utility..

17 Between the two ECV measurement methods, the ETM technique is more error
18 prone as more steps are required for the creation of an ECV map. However, the
19 quality of T1-based ECV map is also dependent on the successful registration of the
20 T1 weighted images necessary to reconstruct each T1 map and the registration of
21 both native and post injection T1 maps. Low resolution acquisition needs to be
22 improved to enable a more accurate permeability and ECV quantification using the
23 ETM method, and to avoid partial volume effects in myocardium edge voxels.
24 However, in the context of the characterization of a diffuse pathology like fibrosis

1 (therefore not located to a specific spot) such low resolution could be sufficient to
2 assess the general state of the myocardial tissue. Furthermore, the low-resolution
3 analysis of the first 2 minutes after injection could help the radiologist to decide
4 whether it worth waiting for a 10 to 15 minutes high-resolution post injection T1 map
5 or even an LGE acquisition. This could therefore be a useful tool to shorten CMR
6 exams and to personalize them to each patient's requirements.

7 The acquisition duration of at least 2 minutes is enough to guarantee an estimation
8 error of V_e inferior to 5% in healthy myocardium, but could lead to slightly more
9 imprecision in the infarcted area, as demonstrated by Pack et al. [18]. In the same
10 study, they also shown an increase of such error if the acquisition duration is below
11 this limit. According to different studies, the optimal DCE duration ranged from 2 to 5
12 minutes [18], [42]–[44]. A longer acquisition duration, e.g. 3 minutes, could improve
13 the precision of V_e estimation (and other ETM parameters) and therefore, reduce the
14 wider distribution of ECV_{ETM} values compared to ECV_{T1} ones as reported in figure 6.
15 This wider distribution could also result from the fact that the ECV_{ETM} parameter is
16 obtained from dynamic data. It is therefore more prone to influences of the local
17 perfusion/permeability regime unlike T1-based ECV, estimated at equilibrium.

18 Despite these limitations, this study demonstrated a clear correlation between
19 compartment parameter estimation from a dynamic perfusion analysis and those
20 measured with the longer static T1-based method. All these results are in agreement
21 with previous related works, but further investigations on a larger population is still
22 needed to fully validate these findings.

1 **5 CONCLUSION:**

2 We presented a complete workflow for the processing of DCE-MRI for compartmental
3 analysis of the myocardial tissue. We were able to demonstrate better registration
4 quality of the presented RC-REG algorithm over the in-line MOCO algorithm. RC-
5 REG algorithm allowed us to compute good quality parametric maps. Resulting
6 ECV_{ETM} parameters exhibited strong correlation with ECV values extracted from
7 MOLLI T1 maps. These results give an additional asset to quantitative cardiac
8 perfusion and permeability MRI in order to assess ECV with a low resolution 2
9 minutes DCE-MRI acquisition against the current 10-15 minutes T1-based method.

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1 **ABBREVIATIONS:**

2 CMR: Cardiac Magnetic Resonance imaging, DCE: Dynamic Contrast Enhancement,

3 ECV: Extracellular volume fraction, EES: Extracellular Extra vascular Space, ETM:

4 Extended Tofts Model, MRI: Magnetic Resonance Imaging, CA: Contrast Agent, RC:

5 Residual Complexity, SD: Standard Deviation, T1w: T1 weighted

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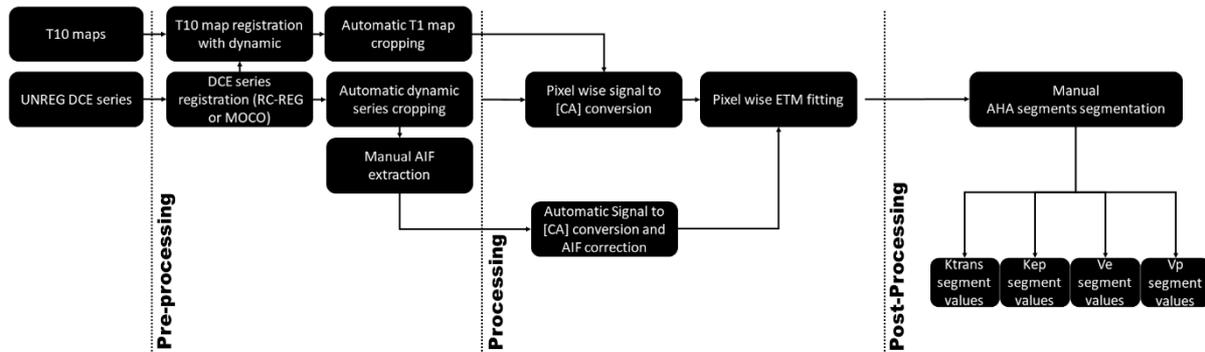
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1 FIGURES AND LEGENDS:

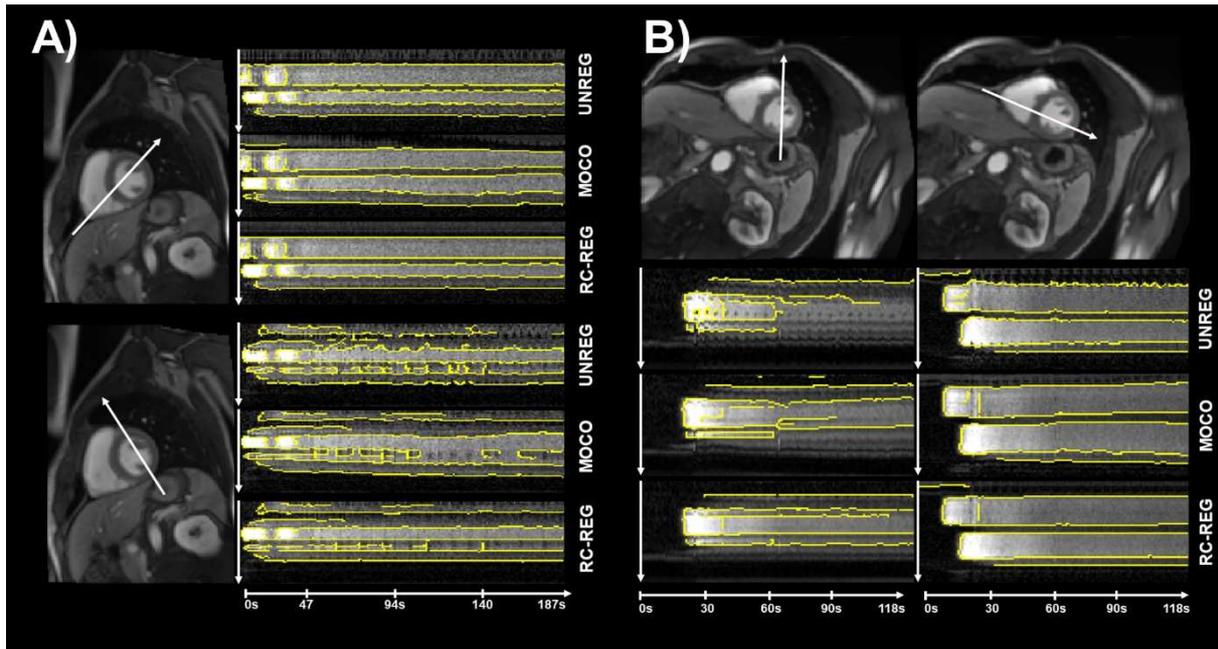
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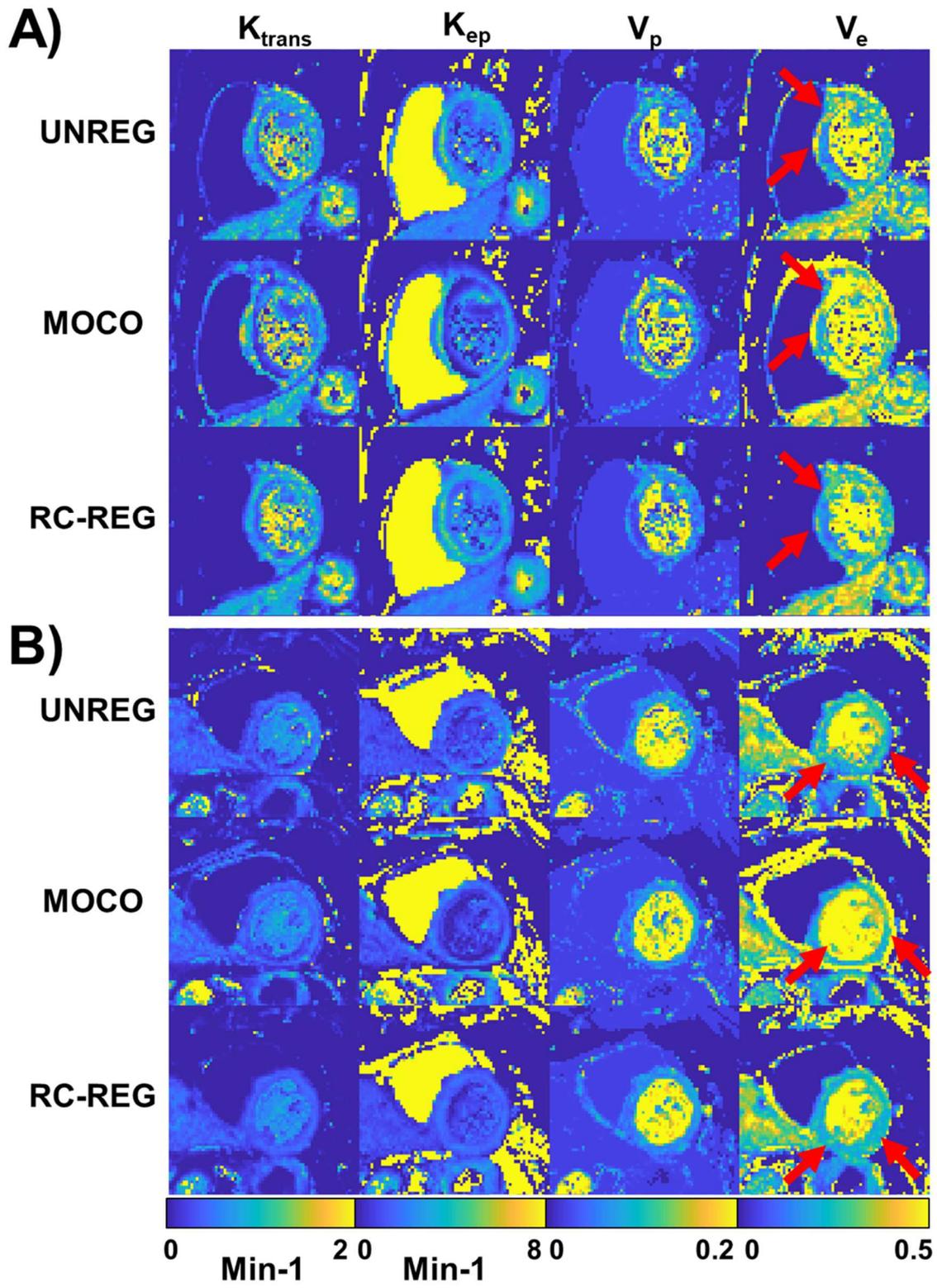
4 **Figure 1:** Framework diagram. The framework is split in 3 major parts: 1) pre-
 5 processing consisting in preparing the necessary data for the processing part; 2)
 6 processing consisting in signal to CA concentration conversion of every pixel from
 7 DCE series, AIF correction and ETM calculation which yields to the processing of the
 8 four permeability maps; and 3) the post-processing part, consisting in the extraction
 9 of the permeability maps parameters with American Heart Association segments.

1 **Figure 2:** RC-REG algorithm diagram. The algorithm is based on the determination
2 of two reference images to register pre-injection series and post-injection series
3 images. Once the series is registered, the SSIM average and SD values of the series
4 are compared to SSIM cutoff values (0.81 and 0.028 respectively). The algorithm
5 iterates until these two conditions are fulfilled.

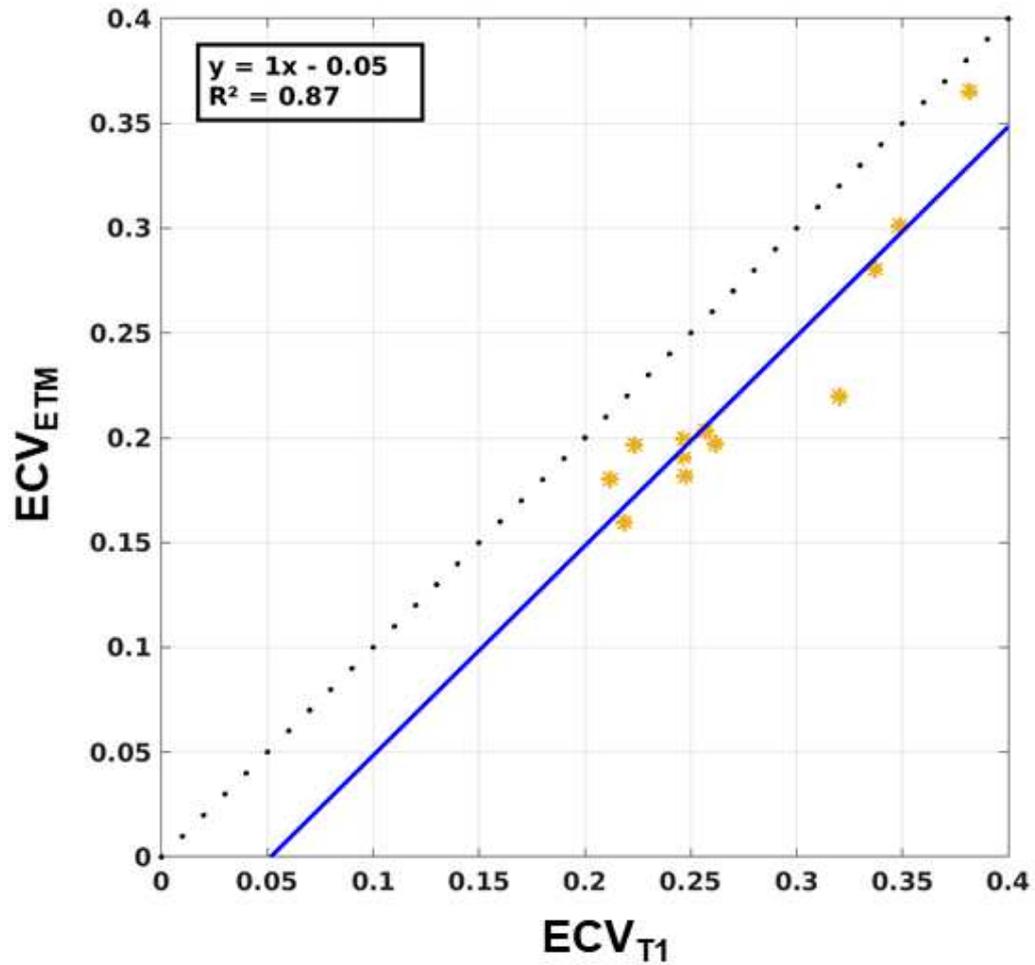


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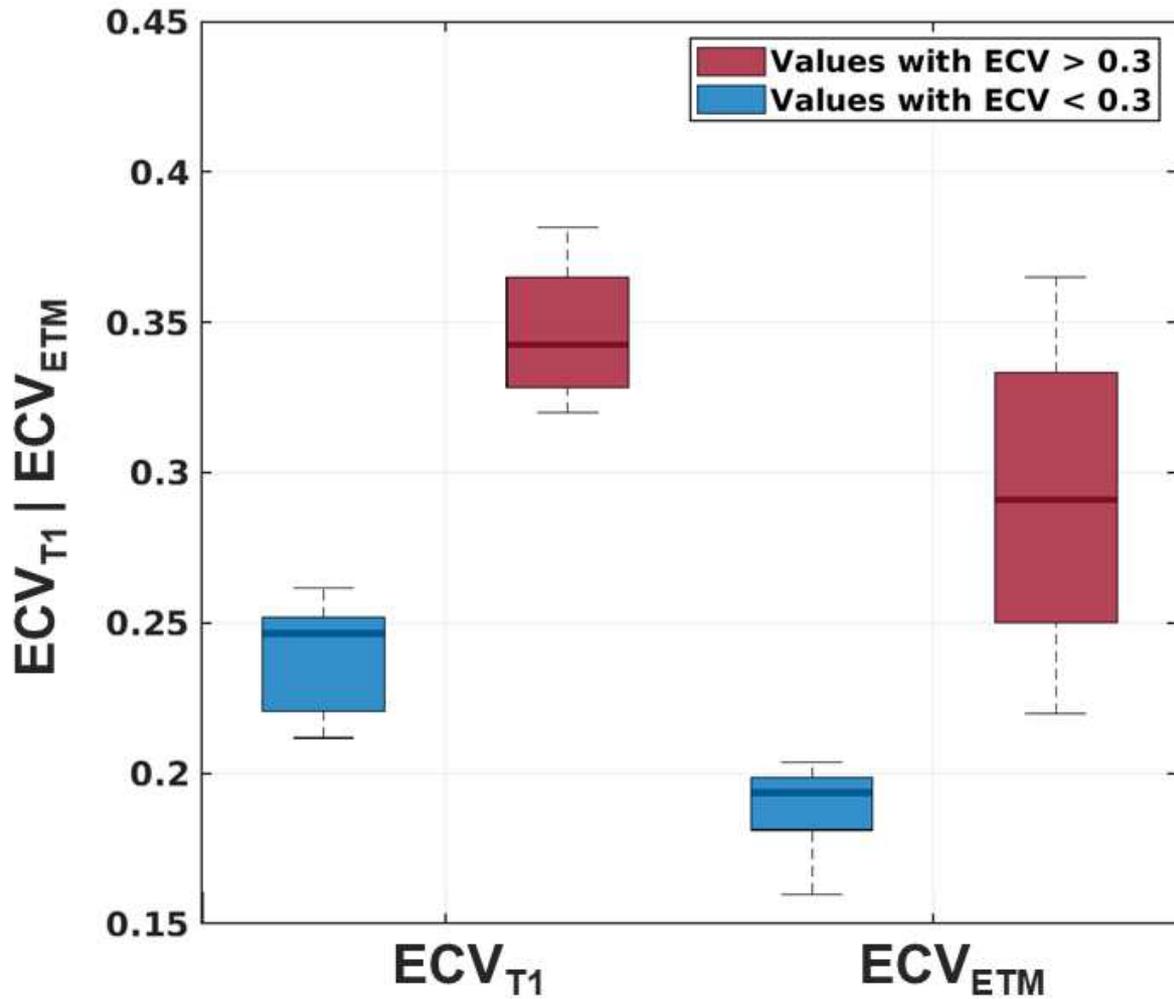
2 **Figure 3:** Example of two slice profiles from two exams with different acquisition
 3 orientation. Intensity based edges detection (canny filter) have been applied on the
 4 line profiles images and are highlighted in yellow. It was used to emphasize both the
 5 registration quality of RC-REG and distortion induced by the MOCO algorithm. A.
 6 First exam slice profiles. It shows on both profiles important distortions brought by the
 7 MOCO algorithm, especially after the first pass. RC-REG series of both slice profiles
 8 does not present distortion such MOCO one. Although we noted a very slight
 9 distortion of the anterior segments on the first slice during the first-pass. B. This
 10 second example shows similar results with A on a different acquisition orientation.
 11 While both MOCO and RC-REG series present a suitable respiratory motion
 12 correction, MOCO series are polluted with blatant distortion over the whole profiles
 13 which are not encountered on RC-REG series.



1 **Figure 4:** Example of two sets of permeability parameters. A and B sets were
2 extracted from UNREG, MOCO and RC-REG DCE data. We can observe a better
3 homogeneity of all parameters values on all maps for RC-REG maps compare to
4 others maps. A. Arrows in V_e maps indicates area were RC-REG map substantial
5 homogenization of V_e values. Two areas in the septal segment seemed to be
6 elevated compare to the rest of the myocardium in UNREG and MOCO V_e maps
7 while values appear to be more homogeneous in RC-REG V_e map. B. Arrows in the
8 inferior segment shows much more noise on UNREG V_e map than on RC-REG V_e
9 map while MOCO V_e map seem to be affected by major distortion of the LV.



- 1 **Figure 5:** ECV_{ETM} and ECV_{T1} myocardial mean values correlation. The RC-REG
- 2 ECV_{ETM} values yielded to a very high correlation factor with ECV_{T1} ones ($R^2 = 0.87$)
- 3 with unity slope. A slight offset equals to -0.05 was nevertheless observed.



- 1 **Figure 6:** Boxplot of distribution of ECV_{ETM} values corresponding to ECV_{T1} above
- 2 and below the cutoff value set to 0.3; ECV_{T1} boxplot is given as reference.
- 3 Permutation test indicated a significant mean difference between the subgroup above
- 4 ($n = 4$) and the subgroup below ($n = 8$) the cutoff value for ECV_{ETM} values.