



HAL
open science

A prospective comparison of dynamic contrast-enhanced MRI and ^{51}Cr -EDTA clearance for glomerular filtration rate measurement in 42 kidney transplant recipients

Benjamin Taton, Renaud de La Faille, Julien Asselineau, Paul Perez, Pierre Merville, Thierry Colin, Christian Combe, Steven Sourbron, Nicolas Grenier

► **To cite this version:**

Benjamin Taton, Renaud de La Faille, Julien Asselineau, Paul Perez, Pierre Merville, et al.. A prospective comparison of dynamic contrast-enhanced MRI and ^{51}Cr -EDTA clearance for glomerular filtration rate measurement in 42 kidney transplant recipients. *European Journal of Radiology*, 2019, 117, pp.209-215. 10.1016/j.ejrad.2019.02.002 . hal-02416091

HAL Id: hal-02416091

<https://inria.hal.science/hal-02416091>

Submitted on 17 Dec 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

A prospective comparison of DCE-MRI and ⁵¹Cr-EDTA for glomerular filtration rate measurement in 42 kidney transplant recipients

Benjamin Taton (PhD, MD)^{1,2,5}

Renaud De La Faille (MD)¹

Julien Asselineau (MSc)³

Paul Perez (MD, PhD)³

Pierre Merville (MD, PhD)¹

Thierry Colin (PhD)^{2,4,5}

Christian Combe (MD, PhD)^{1,6}

Steven Sourbron (PhD)⁷

Nicolas Grenier (MD, PhD)⁸

¹ Centre hospitalier universitaire de Bordeaux, Service de néphrologie, transplantation, dialyse – Groupe hospitalier Pellegrin, France.

² Univ. Bordeaux, IMB, UMR CNRS 5251, F-33400, Talence, France.

³ Centre hospitalier universitaire de Bordeaux, pôle de santé publique, unité de soutien méthodologique à la recherche clinique et épidémiologique, France.

⁴ Bordeaux INP, IMB, FF-33400 Talence, France.

⁵ INRIA Bordeaux Sud-Ouest, MONC team, FF-33400, Talence, France.

⁶ Univ. Bordeaux, Unité INSERM 1026, France.

⁷ Division of medical physics, University of Leeds, United Kingdom.

⁸ Centre hospitalier universitaire de Bordeaux, Service de radiologie et d'imagerie diagnostique et interventionnelle de l'adulte, Groupe hospitalier Pellegrin, France.

Corresponding author:

Benjamin Taton

E-mail: benjamin.taton@chu-bordeaux.fr

Phone: 33 5 56 79 55 38

Fax : 33 5 56 79 61 07

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

A prospective comparison of dynamic contrast-enhanced MRI and ⁵¹Cr-EDTA clearance for glomerular filtration rate measurement in 42 kidney transplant recipients

Abstract

Objectives:

To evaluate the performance of dynamic contrast-enhanced MRI measurement of glomerular filtration rate (GFR) compared with the reference standard technique of urinary clearance of ⁵¹Cr-EDTA.

Patients and methods:

All kidney transplant recipients (KTRs) with an indication for non-urgent contrast-enhanced MRI at our institution were prospectively included between 2008 and 2012. Renographies were acquired by low-dose DCE-MRI then fitted with a two-compartment pharmacokinetic model. MR-GFR was compared with reference isotopic measurements using Bland-Altman diagrams, intraclass correlation coefficient (ICC) and concordance rates.

Results:

Forty-two KTRs (mean age 51.5 years, 26 – 74) were analyzed. Mean estimated GFR was 48.5±27mL/min/1.73m² (24–178 mL/min). The mean bias was +13.2 mL/min (6.4–20.0, +36.9%) ranging from -31.0 mL/min (-41.7%) to +101.4 mL/min (+89.2%) with a

1
2
3
4 large variability (standard-deviation: 22.3 mL/min; limits of agreement: [-30.6 (-43.3—
5
6 18.9); +57.0 (45.3–68.7)]). The ICC was 0.32 (0.02–0.56) and the concordance rate was
7
8 28.6% (14.9–42.2).
9

10
11 **Conclusions:**
12

13
14
15 The large variability of MR-GFR compared with the reference technique precludes its
16
17 use in KTRs, whose anatomical peculiarities make standardization of arterial input
18
19 function (AIF) difficult.
20
21
22
23
24

25 **Keywords:** functional MRI; kidney transplant; glomerular filtration rate; data accuracy.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Abbreviations:

AIF: arterial input function

DCE-MRI: dynamic contrast-enhanced MRI

Gd-CM: gadolinium based contrast media

GFR: glomerular filtration rate

KTR: kidney transplant recipients

1. Introduction

GFR is the hallmark of kidney function in clinical practice. It is generally estimated using formulas that reflect the balance between endogenous synthesis and renal elimination of biological markers (namely creatinine and/or cystatin C) (1). These formulas were built by regression in large specific-population samples. As such, their use to estimate a specific individual's kidney function is often problematic. Measuring the clearance of exogenous markers infused into a patient's bloodstream is considered to be the gold standard for GFR measurement. However, these techniques are not well suited for routine evaluation of kidney function because they are either costly and cumbersome or rely on hypotheses that cannot always be justified. In addition, most often they require nuclear medicine services.

Gadolinium-based contrast media (Gd-CM) have an excellent renal safety profile even in patients with impaired kidney function (2), and have the same pharmacokinetics as the tracers used for clearance measurement techniques (3). Dynamic contrast-enhanced MRI (DCE-MRI) monitors the distribution of Gd-CM in anatomic structures. In association with mathematical models that describe this process, these imaging techniques are promising tools to evaluate kidney function and other physiological parameters of potential interest in nephrology (e.g. renal blood flow, and vascular or tubular transit times). Compared with isotopic methods, MRI provides high-quality anatomic descriptions of the studied organs and as such, it could provide functional maps of native and transplanted kidneys.

Many studies have found encouraging results for native kidneys, in both healthy or diseased (4–11) subjects but biases were highly dependent on both the acquisition

1
2
3
4 protocol and the model used, and error variability was excessively large. Actually, only
5
6 Lim (11) achieved performances compatible with a clinical use of the technique.
7
8

9
10 To our knowledge, the case of KTRs has been studied only by Yamamoto *et al.* (12).
11
12 These authors focused on the diagnostic value of tubular transit times for acute
13
14 rejection, but did not compare MR-GFR with a reference measurement. Investigation of
15
16 KTRs offers a rewarding clinical study group because technically they show only slight
17
18 respiratory movements, and clinically their follow-up often implies iterative graft biopsies,
19
20 making non-invasive procedures highly worthwhile. Moreover, most of them present an
21
22 impaired kidney function, and filtration is almost completely performed by the kidney
23
24 allograft so that there is no need to determine differential filtration to compare MR-GFR
25
26 with reference GFR estimations. This is the first study whose aim was to compare the
27
28 performances of DCE-MRI GFR measurements with ⁵¹Cr-EDTA clearance as a
29
30 reference technique in KTRs.
31
32
33
34
35
36
37

38 **2. Materials and methods**

39 **2.1. Patients**

40
41
42
43
44
45 This prospective study was approved by the institutional review board and the
46
47 interregional ethics authorities (Comité de protection des personnes Sud-Ouest et
48
49 Outre-Mer III), and informed written consent was obtained from all patients. Between
50
51 January 2008 and January 2012, all patients with renal transplantation followed in our
52
53 department, whose medical condition required a non-urgent contrast-enhanced MRI of
54
55 the renal graft, and who had an estimated GFR over 20 mL/min/1.73 m² according to the
56
57
58
59
60
61
62
63
64
65

1
2
3
4 MDRD formula (13), were considered for inclusion to undergo a low-dose MR
5
6 renography.
7

8
9 Patients with contraindications to MR examinations or isotopic determinations of the
10
11 GFR were not included in the study (pregnant or breast-feeding women, patients with
12
13 implanted electronic devices, metallic foreign bodies or surgical clips, severe
14
15 claustrophobia, known intolerance or allergy to Gd-CM).
16
17

18
19 Demographic data was gathered from the patients' medical records and from electronic
20
21 databases. A blood sample was taken to measure creatininemia and hematocrit.
22
23 Isotopic GFR measurement and DCE-MRI examination were performed on the same
24
25 day to avoid any change in kidney function between measurements.
26
27
28

29 30 **2.2. Magnetic resonance imaging** 31

32
33 MRI images were acquired on a 1.5T MRI scanner (ACS-NT - Philips) using a body
34
35 phased-array coil. A three-dimensional saturation-recovery turbo-field echo sequence
36
37 was used with the following parameters: $T_E / T_R = 3.7/6.2\text{ms}$; $\theta = 10^\circ$; slice thickness =
38
39 10mm, no gap; 5 slices; acquisition matrix 60×240 ; reconstructed matrix 256×256 ;
40
41 approximate voxel size: $1.6 \times 1.6 \times 10\text{mm}^3$; parallel imaging (SENSE method, 1.7
42
43 reduction factor). The saturation pulse was applied non-selectively to avoid inflow effects
44
45 within the volume. A coronal oblique section was selected to include both the entire
46
47 kidney allograft on its long axis and the terminal abdominal aorta within the acquisition
48
49 volume, and centered on the renal pedicle. However, in difficult cases, kidney
50
51 parenchyma was given priority over the terminal aorta, provided that an arterial signal
52
53 remained visible in the acquisition volume.
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 The temporal resolution of the sequence was approximately 2 seconds. Before and after
5 injection of the contrast agent, images were acquired iteratively 200 times across 6 min
6
7 40 s without breath holds; the patient was simply asked to breath slowly. As of the 20th
8
9 acquisition, each patient received an intravenous injection of 0.07 mL/kg (33% of a
10
11 standard dose) of gadoterate-meglumine (Dotarem®; Guerbet, Roissy, France) with an
12
13 infusion rate of 2 mL/s, followed by a 20 mL saline flush at 2 mL/s.
14
15
16
17
18

19 In addition to the functional sequence, all subjects underwent standard T1-weighted
20
21 gradient echo and T2-weighted fast spin-echo imaging, and 3D contrast-enhanced MR
22
23 angiography for morphologic assessment.
24
25

26 27 **2.2.1. Data analysis**

28 29 *Image processing*

30
31
32
33 Area under the Gd-CM concentration curve (AUC) was computed for each voxel of the
34
35 functional acquisition. For each patient, a threshold was manually chosen to identify a
36
37 small subset of voxels with the highest AUC in the aorta or the common iliac artery. This
38
39 lead to select a region in the center of the terminal aorta, 2-3 pixels away from aortic
40
41 boundaries. Quite often, the anatomical configuration made it impossible to acquire both
42
43 the graft and the terminal aorta in the same data volume. In such cases, the arterial
44
45 region of interest (ROI) was selected in the common iliac artery or in the upper aorta,
46
47 depending on the place where the highest AUC were found. The AUC image was also
48
49 used to manually delineate the kidney parenchyma (pelvis excluded) on each of the five
50
51 slices available for each patient. Motion of the kidney during the acquisition was ignored.
52
53
54
55
56
57
58 Examples of typical segmentations are shown on Fig. 1.
59
60
61
62
63
64
65

1
2
3
4 The arterial and renal signals were averaged over the corresponding ROI before being
5 used as input for the model-fitting algorithm. Signals corresponding to the images and
6 segmentations given on Fig. 1 are presented as examples on Fig. 2. Kidney volume (V)
7 was computed directly from these ROI as the product of a voxel volume by the number
8 of voxels in the selected region.
9

10
11
12
13
14
15
16
17 Image manipulations and delineations were performed offline using a program
18 developed by (*initials*) using PMI (v. 0.4) and written in IDL (v 6.3).
19
20
21

22 **Compartment model**

23
24
25 The distribution of Gd-CM in the kidney was described using the compartmental model
26 proposed by Sourbron *et al.* (9) and depicted on Fig. 3.
27
28

29
30
31 Gadolinium concentration was assumed to be proportional to the increase of the signal
32 intensity from the basal situation, denoted s_0 , which was computed from the 20 first
33 images: $c(t) \simeq k \times (s(t) - s_0)$. Coefficient k is unknown but cancels out in further
34 computations so that it does not need estimating. The plasma concentration of
35 gadolinium in the aorta was computed from *full blood* concentration by correcting for the
36 hematocrit when available. For eleven patients it was not known and was replaced with
37 the mean value over the whole cohort (35.5%).
38
39
40
41
42
43
44
45
46
47

48
49 The 4 parameters of the model (renal plasma flow, GFR , plasma volume relative to the
50 kidney volume, tubular mean transit time) were determined by fitting the predicted tissue
51 concentration with measured data (likelihood maximization using the Levenberg-
52 Marquardt algorithm (14)). The convergence of the optimization algorithm to a plausible
53 solution was checked visually by comparing the fitted curve with actual data.
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 Computations were implemented in Python and its associated scientific computing
5
6 libraries (15).

10 2.2.2. Isotopic GFR measurement

11
12 Reference GFR values were obtained by measurements of ^{51}Cr -EDTA renal clearance
13 (16). A bolus of 100 μCi (3.7 MBq) ^{51}Cr -EDTA was injected at $t=0$. Each patient was
14
15 asked to drink 5 mL/kg of water at the beginning of the examination and 90mL at $t=60$
16
17 min and asked to void at $t=60$ min. Blood samples were taken at $t=75, 105, 135$ and 165
18
19 min to determine the plasma concentrations of ^{51}Cr -EDTA (P_t). Patients were asked to
20
21 void at $t=90, 120, 150$ and 180 min and to drink 90mL water at each of these time point.
22
23 The volume of urine and urine concentrations of ^{51}Cr -EDTA were determined for each of
24
25 these samples ($V_{t_1-t_2}, U_{t_1-t_2}$).

26
27 The GFR was determined as the mean of four calculations of the urinary clearance of
28
29 ^{51}Cr - EDTA for each time point:

$$30 \quad GFR = \frac{1}{4} \left(\frac{U_{60-90} \times V_{60-90}}{P_{75}} + \frac{U_{90-120} \times V_{90-120}}{P_{105}} + \frac{U_{120-150} \times V_{120-150}}{P_{135}} + \frac{U_{150-180} \times V_{150-180}}{P_{165}} \right)$$

31
32
33 An expert (*initials*) reviewed all these measurements. Patients showing significant
34
35 deviations from this protocol or with large discrepancies between the four clearance
36
37 measurements (coefficient of variation over 10%) were excluded from the study.

51 2.2.3. Statistics

52
53 MR-GFR and ^{51}Cr -EDTA-GFR were compared using Bland-Altman diagrams (17–19),
54
55 intra-class correlation coefficients (ICC) (20) and concordance rates (namely, the
56
57 proportion of patients whose GFR measurements did not differ by more than 5 mL/min
58
59

1
2
3
4 between the two techniques). Linear regression and correlation coefficients were given
5
6 for comparison with previous works. Normality of error distribution in the Bland-Altman
7
8 analysis was tested using Kolmogorov-Smirnov tests.
9

10
11 As we expected an ICC greater than 0.8, we calculated the minimum sample size to be
12
13 55 to obtain a lower bound of the 95% confidence interval of at least 0.6 (this threshold
14
15 is considered to represent good agreement between the investigated techniques) (21).
16
17

18
19 Demographic data are presented as *mean ± standard-deviation* or *median [first; third*
20
21 *quartile]* when appropriate. Comparisons of GFR measurement error between
22
23 subgroups were performed using Wilcoxon tests. Subgroups were defined depending on
24
25 the immunosuppressive regimen, the indication of MRI examinations, and the
26
27 abnormalities reported by the radiologist who interpreted the standard morphological
28
29 acquisitions.
30
31

32
33 Statistics were computed using the R software (version 3.1.2) and the corresponding
34
35 packages (22,23).
36
37
38
39
40
41

42 **3. Results**

43
44

45 Patient selection is shown in the flow diagram in Fig. 4. Sixty-nine patients were initially
46
47 included in the study. Twenty-seven were excluded because MR renography was not
48
49 interpretable (MRI artefacts or poor positioning of the acquisition volume resulting in
50
51 sequences without dependable arterial signal) (15 patients), or because their isotopic-
52
53 GFR calculation was untrustworthy (12 patients). Finally, 42 patients were analysed (29
54
55 men, 13 women; mean age 51.5 years; age range 26—74) (Table 1). The median time
56
57
58
59
60
61
62
63
64
65

1
2
3
4 from kidney transplantation to isotopic measurements and MRI examination was
5
6 397 [113; 1145] days.
7
8

9
10 For most patients, acquiring both the entire kidney and the terminal abdominal aorta at
11
12 the same time proved impossible and arterial ROI had to be selected in the upper aorta
13
14 or in the common iliac artery: the ROI was taken in the aorta for 35/42 (83.3%) patients,
15
16 and in the iliac artery for 7/42 (16.7%) patients. The size of the arterial ROI was on
17
18 average 62 ± 28 voxels (median: 54.5, range: 23—154) for the aortic region, and
19
20 8878 ± 2318 voxels (median: 8089.5, range: 5617—15262) for the kidney parenchyma
21
22 (average volume of the kidney: 203 ± 50 mL; median: 192; range: 135—321).
23
24
25
26

27
28 Mean estimated GFR (MDRD formula) of our patients was 48.5 ± 27 mL/min/ 1.73m^2
29
30 (eGFR range: from 24 to 178). Mean GFR measured by the isotopic reference technique
31
32 was 41.8 ± 14.5 mL/min (EDTA-GFR range: from 18.3 to 81.1). Mean GFR measured by
33
34 DCE-MRI was 55.0 ± 26.0 mL/min (MR-GFR range: from 23.9 to 170.1 mL/min). As
35
36 plasma samples were available, we also determined the plasma clearance of ^{51}Cr -EDTA
37
38 according to Bröchner-Mortensen's technique (24) as an alternative reference
39
40 measurement. As already stated in previous works (25), the two techniques were in
41
42 good agreement, plasma clearance being slightly higher than renal clearance (mean
43
44 difference between measurements: 4.3 ± 7.6 mL/min). The use of either reference
45
46 technique did not change the conclusion of our study (see supplemental material Fig. S3
47
48 and S4).
49
50
51
52
53

54
55
56 The comparison between MR-GFR and the reference method is depicted in Fig. 5.
57
58 There was a fair correlation between both measurements ($p < 0.001$, $r = 0.52$). The
59
60
61
62
63
64
65

1
2
3
4 regression line of MR-GFR against EDTA-GFR had a slope of 0.92 and an intercept
5
6 of 16.5 mL/min. Our measurement protocol lead to a large overestimation of the GFR
7
8 compared with the reference technique. The mean difference with the reference
9
10 technique was $+13.2 \pm 22.3$ mL/min (6.4—20.0, +36.9%) with a large variability (limits of
11
12 agreement: [-30.6(-42.3—18.9); 57.0(45.3—68.7)]). The ICC was 0.32 (0.02—0.56), far
13
14 below the 0.6 threshold for satisfactory agreement between the two techniques. The
15
16 concordance rate was 28.6% (14.9—42.2). Finally, on average, the systematic bias was
17
18 slightly increasing with the GFR value (+0.28 mL/min per mL/min increase).
19
20
21
22
23

24
25 When comparing subgroups of patients depending on their immunosuppressive
26
27 regimen, the indication for the MRI, or the morphological abnormalities, no specific
28
29 characteristic presented a significant association with larger measurement errors
30
31 (Fig. 6).
32
33

34
35 To investigate the influence of ROI selection on measured GFR, we restricted our
36
37 analysis to the patients for whom the AIF could be determined from the aorta (36/42,
38
39 86% of patients). In these patients, the mean bias was 11.6 ± 18.3 mL/min, with
40
41 [-24.2(-34.6—13.8); +47.6(37—57.8)] limits of agreement (vs. 13.2 ± 22.3 mL/min in the
42
43 whole cohort). The decrease in error variability was not statistically significant ($p=0.38$
44
45 for the modified one-sided paired Pitman-Morgan test). In a second experiment the AIF
46
47 was determined from the iliac artery in a region as close as possible of the implantation
48
49 of the kidney allograft artery and the GFR was computed using this new AIF (this was
50
51 possible for 37/42 (88%) patients). In comparison with the aortic AIF, the mean bias was
52
53 24.2 ± 25.5 mL/min (vs. 11.6 ± 18.3) with [-25.8(-40.3—11.3); +74.3(59.8—88.8)] limits of
54
55 agreement. The decrease in error variability did not reach statistical significance
56
57
58
59
60
61
62
63
64
65

1
2
3
4 (p=0.26). The associated Bland-Altman diagrams are presented in the supplemental
5
6 material (Fig. S2).
7
8
9

10 11 **4. Discussion** 12 13

14
15 This is the first study performed in a cohort of KTRs for whom non-invasive GFR
16
17 measurement would be extremely worthwhile and who show a wide range of GFR
18
19 values measured with a reference technique. We chose to exclude all the patients with
20
21 doubtful isotopic measurements (12/69) to reinforce the value of this reference
22
23 technique, keeping only trustworthy results.
24
25
26

27
28 Overall, while using DCE-MRI to estimate GFR was feasible for KTRs, compared to the
29
30 reference technique, DCE-MRI strongly overestimated GFR and exhibited a large
31
32 variability with poor intra-class correlation coefficients and low concordance rates.
33
34

35
36 Whereas there is no other experience in the literature on KTRs for comparison, our
37
38 results are somewhat consistent with previously published work on native kidneys but
39
40 exhibit a higher systematic bias and larger error variability.
41
42

43
44 Using a Rutland-Patlak technique in 28 diseased subjects, Hackstein *et al.* (5) found a
45
46 correlation coefficient $r=0.86$ between iopromide clearance measurements and MR-
47
48 GFR, and a standard deviation from the regression line of 14.8 mL/min. In 39 patients
49
50 with a large range of GFR, Buckley *et al.* (6) also found a strong correlation between
51
52 isotopic reference measurements and MR-GFR (Spearman's ρ : 0.81). In another
53
54 population of diseased subjects, using and slightly different pharmacokinetic models but
55
56 the same acquisition protocol, Lee *et al.* (7) and Zhang *et al.* (8) obtained consistent
57
58
59
60
61
62
63
64
65

1
2
3
4 results: mean bias of -11.8 and -18.1 mL/min, and variability of ± 13.7 and ± 13.9 mL/min
5
6 respectively in comparison with isotopic GFR determination (correlation coefficient was
7
8 $r=0.82$). In the same population, with the same acquisition protocol and reference
9
10 technique but with 8 different pharmacokinetic models, Bokacheva *et al.* (9) also found a
11
12 good correlation between MR-GFR and reference measurements (correlation
13
14 coefficients ranging from 0.74 to 0.85). Nonetheless, biases were highly dependent on
15
16 the model used, ranging from -52% to -2.5%. Vivier *et al.* (11) experimented other
17
18 acquisition and post-treatment protocols with variants of the pharmacokinetic model by
19
20 Zhang *et al.* in 20 patients with cirrhosis. Depending on the variant of the model and the
21
22 orientation of the slice used for the post-processing, they found a median bias ranging
23
24 from -7.7 to -4.1 mL/min, with a root mean square error between 12.8 and 12.9 mL/min.
25
26 The most promising results were obtained by Lim *et al.* in diseased patients with a wide
27
28 range of GFR (12). Compared with reference isotopic GFR measurements, their protocol
29
30 achieved a non-significant mean bias of -0.7 mL/min and variability of ± 5.86 mL/min,
31
32 small enough to be compatible with clinical use.
33
34
35
36
37
38
39
40

41 Discrepancies of our results with previous works could be explained both by anatomic
42
43 characteristics of transplanted kidneys compared to natives ones and by our workflow
44
45 with respect to these characteristics.
46
47

48
49 In term of anatomic characteristics, in contrast with native kidneys, renal allografts
50
51 exhibit a large variability in their anatomical configurations. This problem, which has
52
53 been highly underestimated, made very difficult to combine an accurate positioning of
54
55 the acquisition slab along the long axis of the graft and inclusion of the terminal aorta or
56
57 of the common iliac artery. As illustrated on Fig. 2, this resulted in difficulties to achieve
58
59
60
61
62
63
64
65

1
2
3
4 standardized and reproducible ROIs selection for the AIF. The 10mm thick coronal slices
5
6 also favoured partial volume effects (PVE), mainly when AIF had to be sampled on iliac
7
8 arteries instead of aorta, resulting in an underestimation of the AIF, and subsequently, in
9
10 an overestimation of GFR. As the importance of PVE depends on the position of the
11
12 acquisition matrix with respect to the arteries, which cannot be controlled, this probably
13
14 accounts for a large part of the higher variability we noticed compared with
15
16 measurements on native kidneys. The increase in the bias noticed when using an AIF
17
18 sampled from the iliac arteries (see supplemental material, Fig. 4), which are more
19
20 prone to PVE due to their smaller diameter, is consistent with this hypothesis. Finally,
21
22 the close proximity of renal parenchyma with iliac vessels could also produce PVE,
23
24 mixing signals coming from both structures.
25
26
27
28
29
30

31
32 Considering the model of Gd-CM pharmacokinetics, the interstitial compartment induces
33
34 large overestimation of GFR. This hypothesis is consistent with the results obtained in
35
36 most previous studies since the most negative biases are noticed mostly in the patients
37
38 with the highest reference GFR measurements. In our cohort, most patients had an
39
40 impaired kidney function, a setting often associated with fibrosis in KTRs, which could
41
42 explain the observed positive bias. However, no histological evaluation of the interstitial
43
44 volume was performed, and this hypothesis remains speculative.
45
46
47
48

49
50 Also, in our population of KTRs, the whole filtration function was attributed the
51
52 transplant. However, some patients actually have a residual function from their native
53
54 kidneys that presumably ranges from 0 to 10 mL/min. While this hypothesis is not
55
56 consistent with GFR overestimation, it cannot be ruled out and may explain part of the
57
58 large variability we noticed.
59
60
61
62
63
64
65

1
2
3
4 At last, kidney motion was ignored because transplants are located far away from the
5
6 diaphragm muscle. However spontaneous voluntary or digestive motions actually
7
8 occurred and have inescapably increased error variability. This suggests that, even for
9
10 KTRs, motion correction could prove beneficial to obtain reproducible results.
11
12
13
14

15 **5. Conclusion**

16
17
18
19 This first study on the performance of MR-measurement of GFR in KTRs with respect to
20
21 a reference technique shows that, even if kidney grafts are unique, less mobile and
22
23 more superficially located, an overestimation and a large variability still precludes its use
24
25 in clinical practice without significant improvements. Anatomical constraints make the
26
27 standardization of ROI selection more difficult than in native kidneys and lead to larger
28
29 and unpredictable partial volume effects. These characteristics hamper an accurate and
30
31 reproducible measurement of AIF and probably contribute for a large part to bias and
32
33 variability.
34
35
36
37
38
39
40

41 **6. Acknowledgements**

42
43
44
45 Blinded for submission.
46
47
48
49

50 **References**

- 51
52
53
54 1. Levey A, Inker L, Coresh J. GFR estimation: from physiology to public health. *Am*
55 *J Kidney Dis.* 2014;63:820–834.
56
57 2. Soyer P, Dohan A, Patkar D, Gottschalk A. Observational study on the safety
58 profile of gadoterate meglumine in 35,499 patients: the SECURE study. *J Magn Reson*
59 *Imaging.* 2017;45(4):988–997.
60
61
62
63
64
65

3. Choyke P, Austin H, Frank J, Girton M, Diggs R, Dwyer A, et al. Hydrated clearance of gadolinium-DTPA as a measurement of glomerular filtration rate. *Kid Int.* 1992;41:1595–1598.
4. Hackstein N, Heckrodt J, Rau W. Measurement of single-kidney glomerular filtration rate using a contrast-enhanced dynamic gradient-echo sequence and the Rutland-Patlak plot technique. *J Magn Reson Im.* 2003;18:714–725.
5. Buckley D, Shurrab A, Cheung C, Jones A, Mamtora H, Kalra P. Measurement of single kidney function using dynamic contrast-enhanced MRI: comparison of two models in human subjects. *J Mag Reson Imaging.* 2006;1117–1123.
6. Lee V, Rusinek H, Bokacheva L, Huang A, Oesingmann N, Chen Q, et al. Renal function measurements from MR renography and a simplified multicompartment model. *Am J Physiol Ren Physiol.* 2007 May;292:F1548–F1559.
7. Zhang J, Rusinek H, Bokacheva L, Lerman L, Chen Q, Prince C, et al. Functional assessment of the kidney from magnetic resonance and computed tomography renography: impulse retention approach to a multicompartmental model. *Magn Reson Med.* 2008 Feb;59(2):278–288.
8. Bokacheva L, Rusinek H, Zhang J, Chen Q, Lee V. Estimates of glomerular filtration rate from MR renography and tracer kinetics models. *J Magn Reson Imaging.* 2009;29:371–382.
9. Sourbron S, Michaely H, Reiser M, SO S. MRI-measurement of perfusion and glomerular filtration in the human kidney with a separable compartment model. *Invest Radiol.* 2008 Jan;43(1):40–48.
10. Vivier P, Storey P, Rusinek H, Zhang J, Yamamoto A, Tantilillo K, et al. Kidney function: glomerular filtration rage measurement with MR renography in patients with cirrhosis. *Radiology.* 2011;259(2):462–470.
11. Lim S, Chrysochou C, Buckley D, Kalra P, Sourbron S. Prediction and assessment of responses to renal artery revascularization with dynamic contrast-enhanced magnetic resonance imaging: a pilot study. *Am J Physiol Ren Physiol.* 2013;305(5):F672–F678.
12. Yamamoto A, Zhang J, Rusinek H, Chandarana H, Vivier P, Babb J, et al. Quantitative evaluation of acute renal transplant dysfunction with low-dose three dimensional MR renography. *Radiology.* 2011;260(3):781–789.
13. Lenihan C, O’Kelly P, Mohan P, Little D, Walshe J, Kieran N, et al. MDRD-estimated GFR at one year post-renal transplant is a predictor of long-term graft function. *Ren Fail.* 2008;30:345–352.
14. Press W, Teukolsky S, Vetterling W, Flannery B. Numerical recipes: the art of scientific computing. In Cambridge University Press; 2007. p. 773–839.
15. Jones E, Oliphant T, Peterson P, others. SciPy: Open source scientific tools for Python [Internet]. 2001. Available from: <http://www.scipy.org/>
16. Soveri I, Berg U, Björk J, Elinder C, Grubb A, Mejare I, et al. Measuring GFR: a systematic review. *Am J Kid Dis.* 2014;64(3):411–424.

1
2
3
4 17. Bland J, Altman D. Statistical methods for assessing agreement between two
5 methods of clinical measurement. Lancet. 1986 Feb;307–310.
6
7 18. Hamilton C, Stamey J. Using Bland-Altman to assess agreement between two
8 medical devices – don't forget the confidence intervals! J Clin Monit Comput.
9 2007;21(6):331–333.
10
11 19. Euser A, Dekker F, le Cessie S. A practical approach to Bland-Altman plots and
12 variation coefficients for log-transformed variables. J Clin Epidemiol. 2008;61(10):978–
13 982.
14
15 20. Bartko J. The intraclass correlation coefficient as a measure of reliability. Physiol
16 Rep. 1966;19:3–11.
17
18 21. Bonett D. Sample size requirements for estimating intraclass correlations with
19 desired precision. Stat Med. 2002;21:1331–1335.
20
21 22. Team RC. R: A language and environment for statistical computing [Internet].
22 Vienna, Austria: R Foundation for Statistical Computing; 2013. Available from:
23 <http://www.R-project.org>
24
25 23. Gamer M, Lemon J, Fellows I, Singh P. irr: various coefficients of interrater
26 reliability and agreement [Internet]. 2012. Available from: [http://CRAN.R-](http://CRAN.R-project.org/package=irr)
27 [project.org/package=irr](http://CRAN.R-project.org/package=irr)
28
29 24. Bröchner-Mortensen J. A simple method for the determination of glomerular
30 filtration rate. Scand J Clin Lab Invest. 1972;30:271–274.
31
32 25. Moore A, Park-Holohan S, Blake G, Fogelman I. Conventional measurements of
33 GFR using 51Cr-EDTA overestimate true renal clearance by 10 percent. Eur J Nucl
34 Med. 2003;30(1):4–8.
35
36
37
38
39

40 **Tab. 1. Demographic characteristics of the 42 kidney-transplant recipients**
41 **and 34 donors analyzed.** The number of patients for which the data were available is
42 given in the third column (*n*).
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 **Fig. 1. Examples of manual delineations of arterial and parenchymal region of**
5 **interest (red regions) on the AUC images.** Left: case where both the terminal aorta
6 and the kidney allograft could be included in the same acquisition volume. Isotopic GFR
7 was 34.4 mL/min, MR-GFR was 60.7 mL/min. Right: case where the anatomical
8 configuration made this impossible. In this case, the distinction between the common
9 iliac aorta and the allograft parenchyma is very difficult, due to anatomical proximity and
10 partial volume effects (white arrows). Isotopic GFR was 81.1 mL/min, MR-GFR was 69.4
11 mL/min.
12
13

14
15 **Fig. 2. Gadolinium concentration time curves in the blood (red, solid), the allograft**
16 **parenchyma (black, dashed), and predicted by the model with the optimal**
17 **parameters (purple, dash-dotted).** The presented signals correspond to the mean
18 value of the corresponding ROIs, as presented on Fig. 1. Left (top), and Fig. 1. Right
19 (bottom).
20
21

22
23 **Fig. 3. Pharmacokinetic model used in the study.** Gadolinium enters the vascular
24 compartment (denoted p , with a volume v_p) with arterial plasma with a flow that
25 corresponds to the renal plasmatic flow (RPF) and a concentration $c_A(t)$. Part of it is
26 filtered into a tubular compartment (denoted e , with a volume v_e) with a coefficient that
27 corresponds to the glomerular filtration rate (GFR). The remaining ($RPF - GFR$) is
28 returned to the general circulation. The filtered gadolinium is subsequently eliminated
29 into the bladder with a transit time that is a parameter of the model. The dashed line
30 represents reabsorption of gadolinium-free fluid.
31
32

33
34 **Fig. 4. Flow-chart of the study.** Twelve patients were excluded because their
35 reference measurement was not reliable (large discrepancies between the four
36 measurements of the renal clearance of $^{51}\text{Cr-EDTA}$). Fifteen patients were excluded
37 because the MRI acquisition was not suitable for GFR measurements (MRI artifacts, bad
38 positioning of the acquisition volume).
39
40

41
42 **Fig. 5. Relationship between MR-GFR and the reference measurements.** Top-left:
43 linear regression of MR-GFR against $^{51}\text{Cr-EDTA}$ clearance: slope was 0.92, intercept
44 was 16.5 mL/min, correlation coefficient was 0.52. The regression line is plotted with a
45 solid line. The (ideal) identity line is plotted with a dashed line. Each point corresponds
46 to one the measurements for one patient. Top-right: Bland-Altman diagram. The dashed
47 line represents the mean bias over the whole cohort (+13.2 mL/min). Dotted lines
48 represent the limits of agreement ([-30.6; +57.0]). Normality of errors was tested using a
49 Kolmogorov-Smirnov test ($p = 0.21$). The ideal no-difference line is draw with a solid
50 line. Each point corresponds to the measurement for one patient. Bottom-left: Bland-
51 Altman analysis with log-transformed data (Kolmogorov-Smirnov test: $p = 0.90$). Bottom-
52 right: limit of agreement computed from Bland-Altman analysis of the log-transformed
53 data. On average, the systematic bias is slightly increasing with the GFR (+0.28 mL/min
54 per mL/min increase). The dashed line corresponds to the mean ratio between the bias
55 and the mean of EDTA clearance and MR-GFR. The dotted lines correspond to the limit
56 of agreements of the ratio, as depicted in the bottom-left figure.
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Fig. 6. Discrepancies between EDTA clearance and MR-GFR (relative values) depending on the use of calcineurin inhibitors in the patient's immunosuppressive regimen (Wilcoxon exact test: $p = 0.32$), the indication of the MRI examinations (exact Wilcoxon tests: $p = 0.08, 0.68, 0.99, 0.42, 0.84$ for hypertension, vascular anomaly, urological anomaly, renal mass and kidney failure respectively), and on the abnormalities reported by the radiologist (Wilcoxon exact test: $p = 0.85, 0.06, 0.71$ and 0.08 for the association with renal artery stenosis, dilation of pelvi-caliceal cavities, perirenal collection and perfusion defect respectively).

6. Acknowledgements

This study was supported by a public grant from the French National Research Agency (ANR) within the context of the “Investment for the Future” program, referenced ANR-10-LABX-57 and named TRAIL, the French State managed by the ANR referenced ANR-10-IDEX-03-02, named IdEx Bordeaux CPU, and the Centre Hospitalier Universitaire de Bordeaux (AOI-05). The authors thank Corinne Castermans, for her help in data managing and Pippa McKelvie-Sebileau, MSc, Bordeaux, France, for medical editorial assistance in English.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

| Characteristics | Value | <i>n</i> |
|------------------------------------|------------------------|----------|
| Patient | | |
| age (yrs) | 51.5±12.9 | 42 |
| males / females | 29 (69.1%) / 13(30.9%) | 42 |
| eGFR (mL/min/1.73m ²)* | 48.5±27.0 | 42 |
| hematocrit (%) | 35.5±5.3 | 31 |
| Kidney donor | | |
| age (yrs) | 50.6±16.6 | 34 |
| males | 17 (50%) | 34 |
| females | 17 (50%) | 34 |
| Elapsed time from graft to MRI | 397 [113; 1445] | 42 |
| Immunosuppressive regimen | | |
| calcineurin inhibitors | 37 (88.1%) | 42 |
| Indication for MRI examination | | |
| vascular anomaly | 24 (57.2%) | 42 |
| urologic anomaly | 8 (19%) | 42 |
| arterial hypertension | 3 (7.1%) | 42 |
| kidney failure | 2 (4.8%) | 42 |
| renal mass | 2 (4.8%) | 42 |
| other | 3 (7.1%) | 42 |

*eGFR according to the MDRD formula

Tab. 1. Demographic characteristics of the 42 kidney-transplant recipients and 34 donors analyzed. The number of patients for which the data were available is given in the third column (*n*).

Figure 1
[Click here to download high resolution image](#)

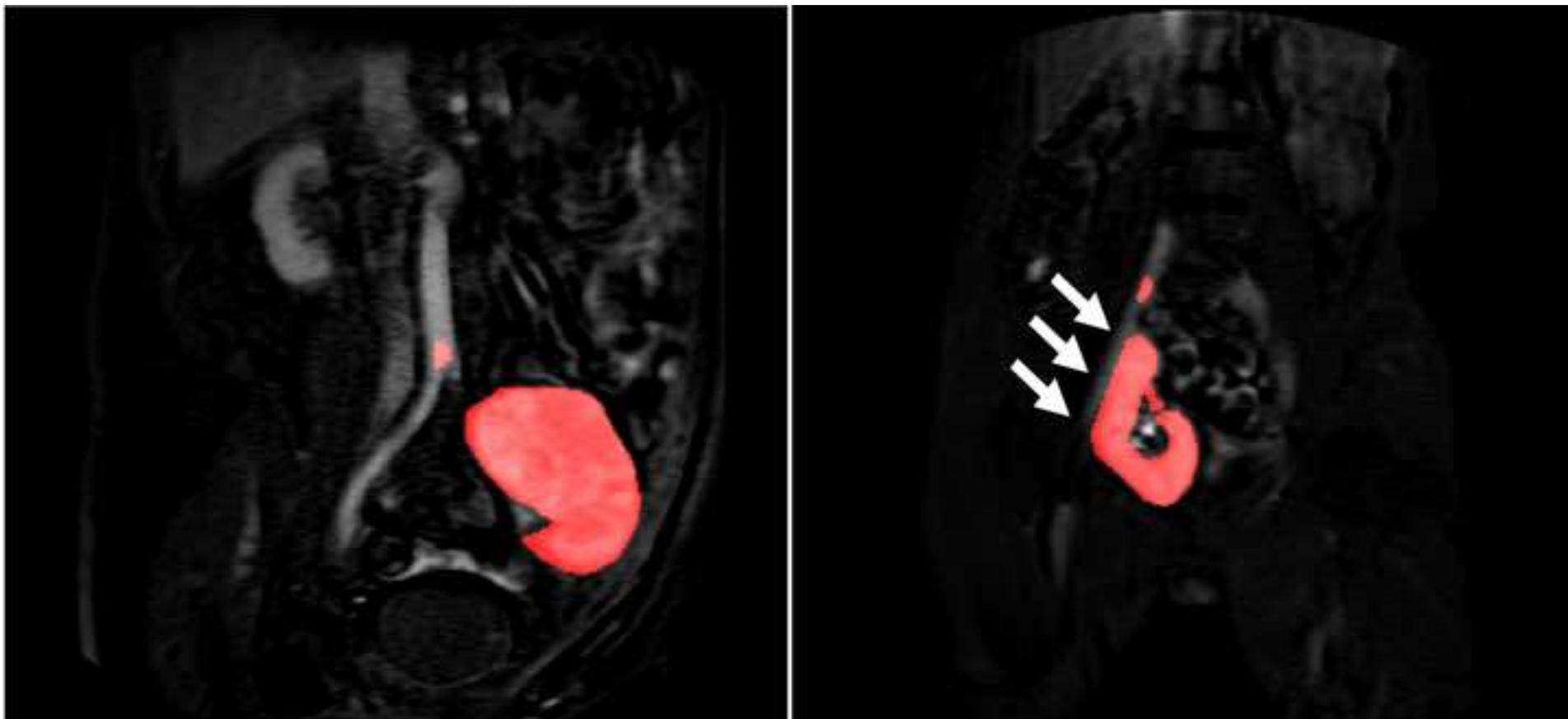


Figure 2

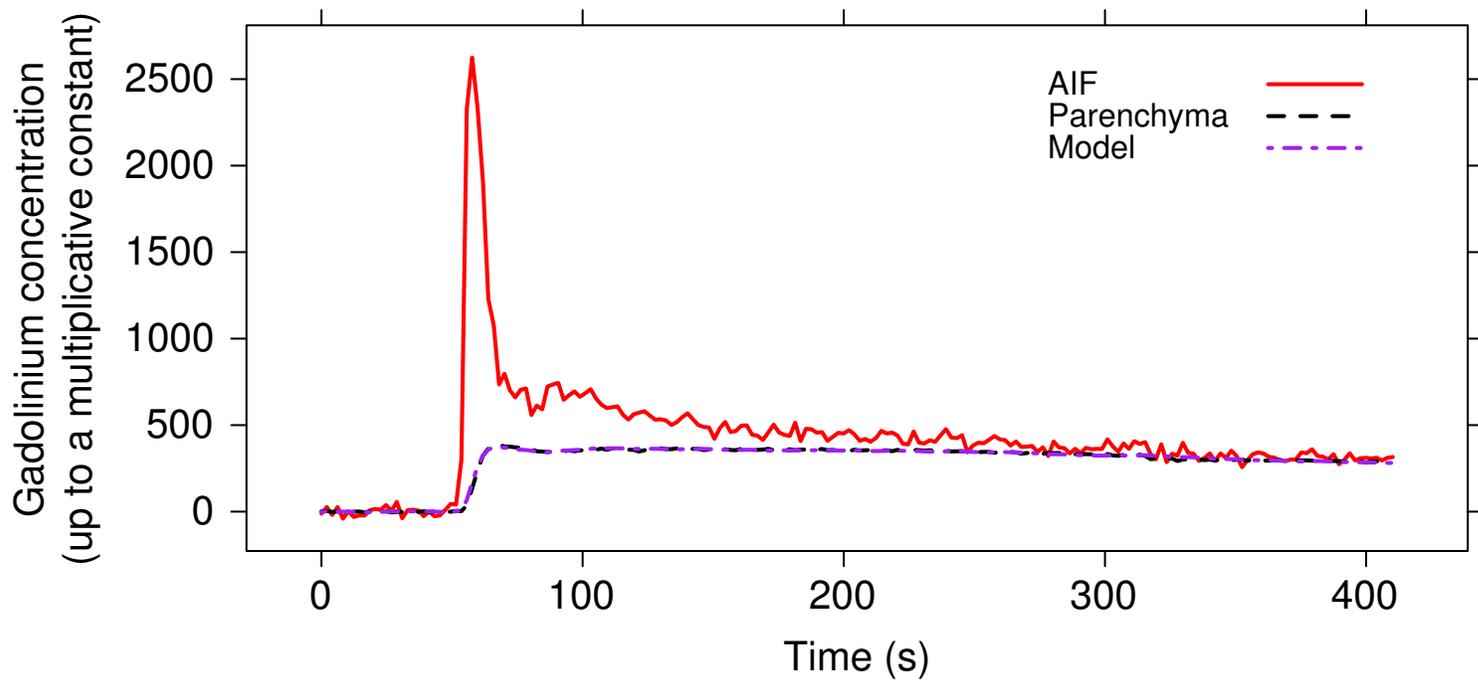
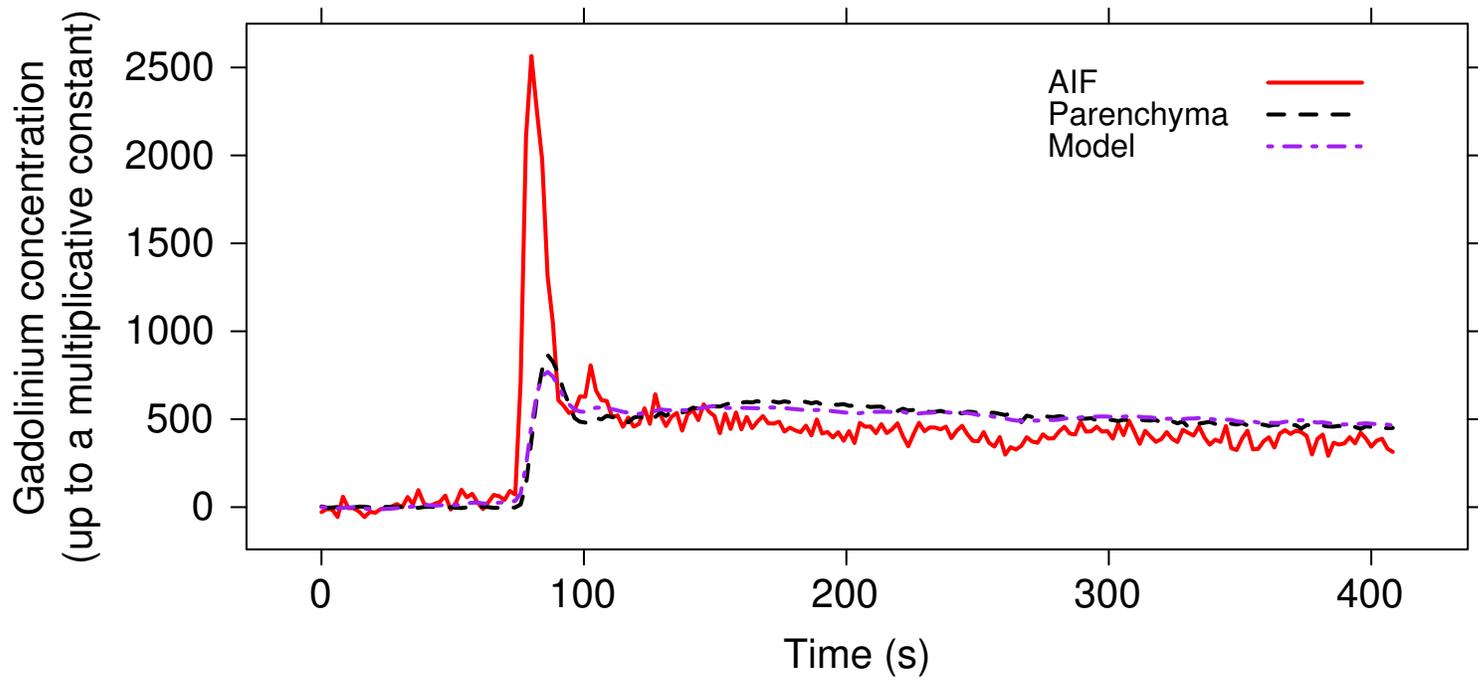


Figure 3

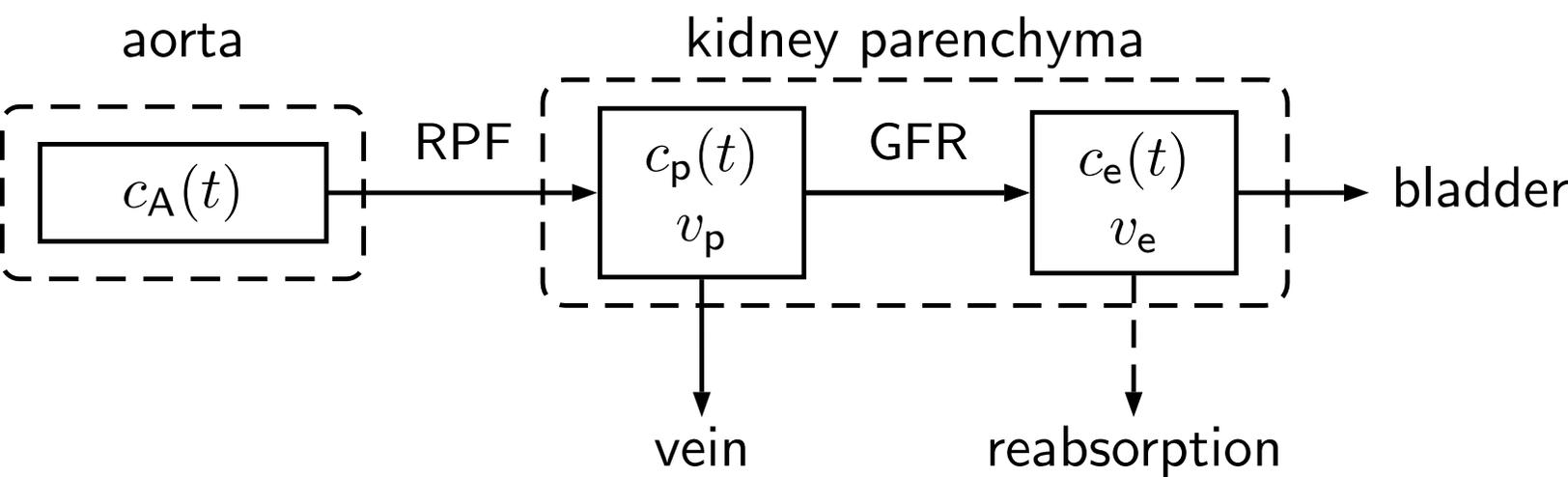


Figure 4

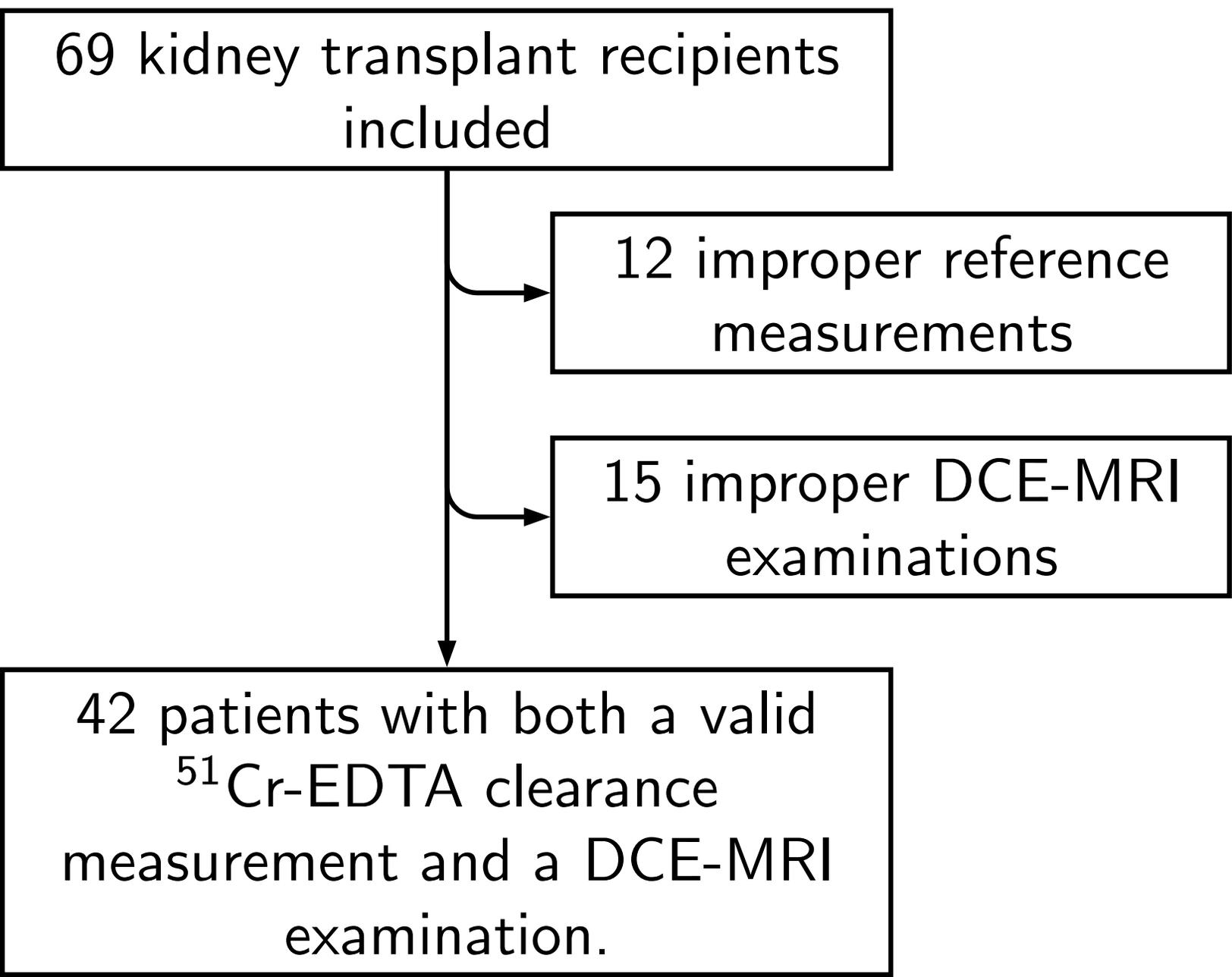


Figure 5

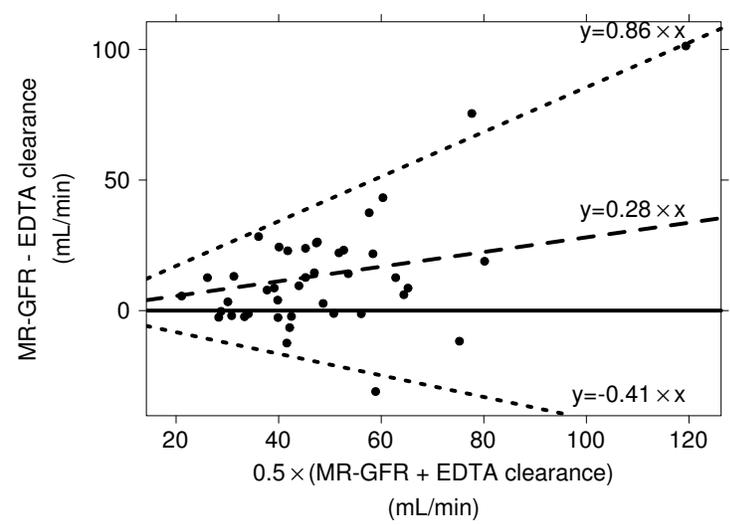
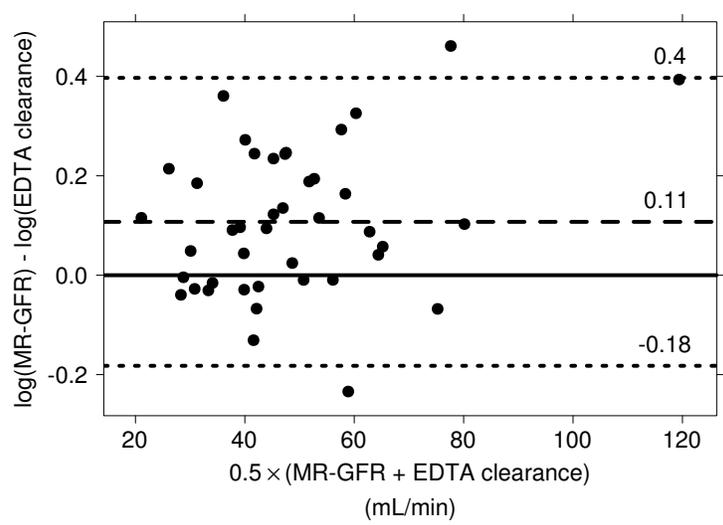
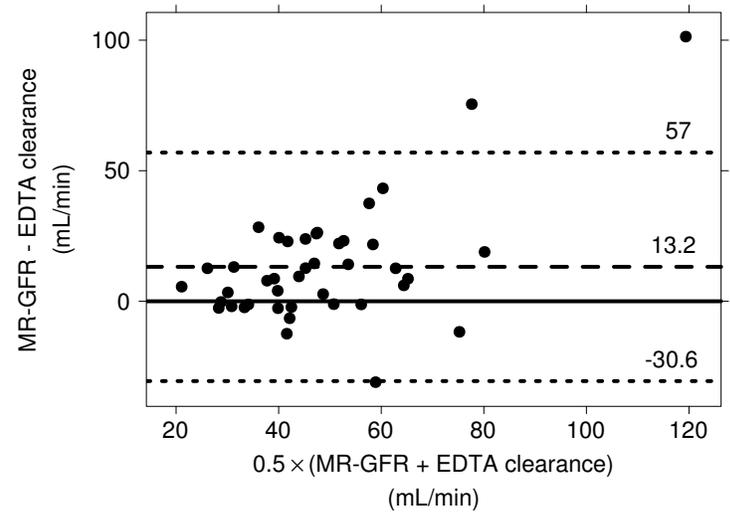
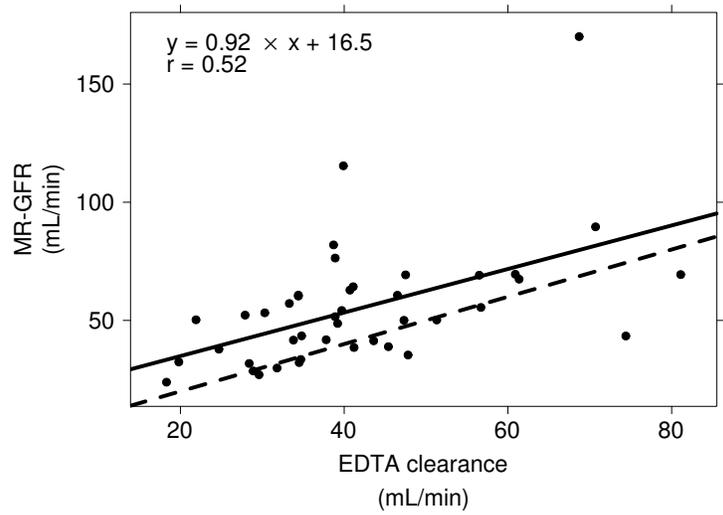
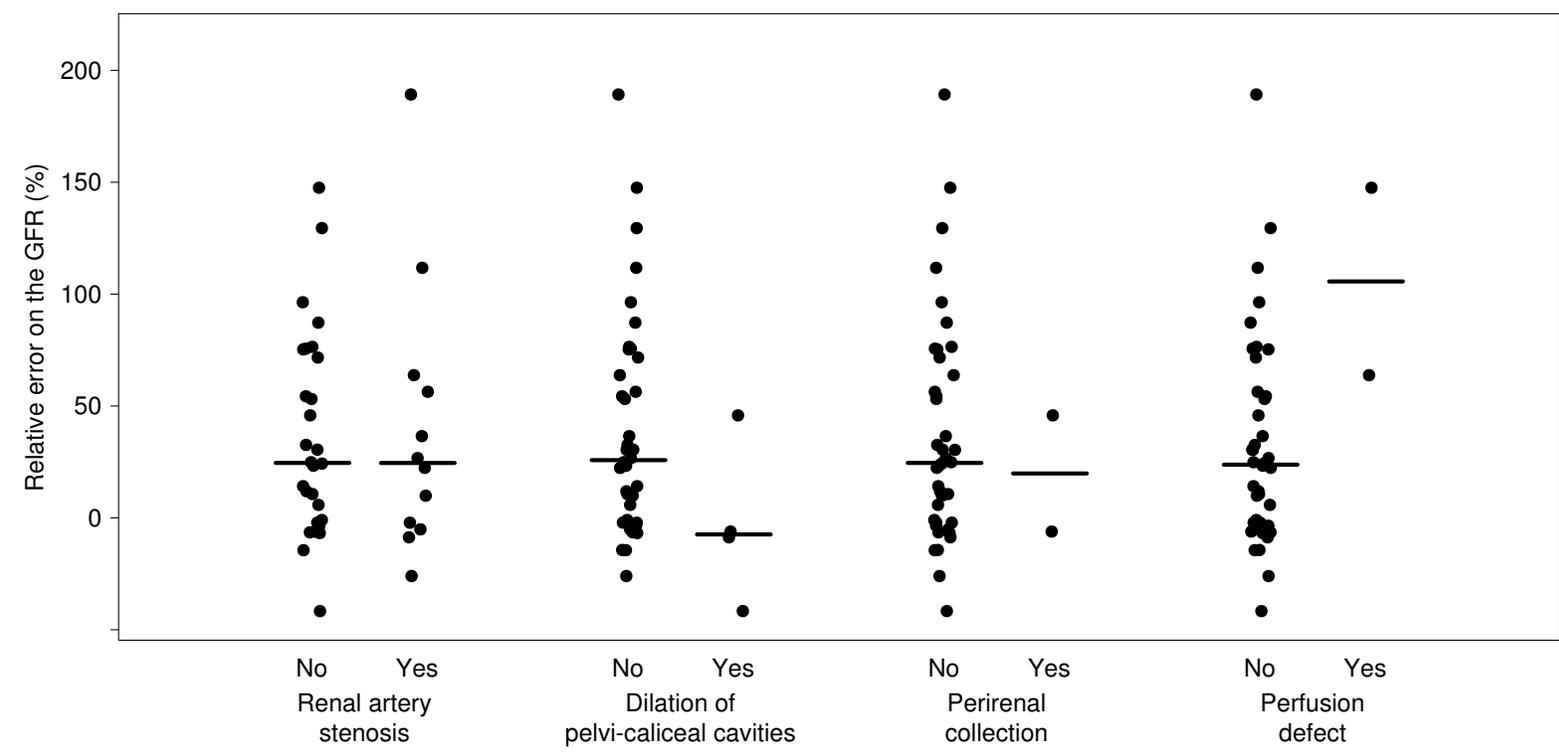
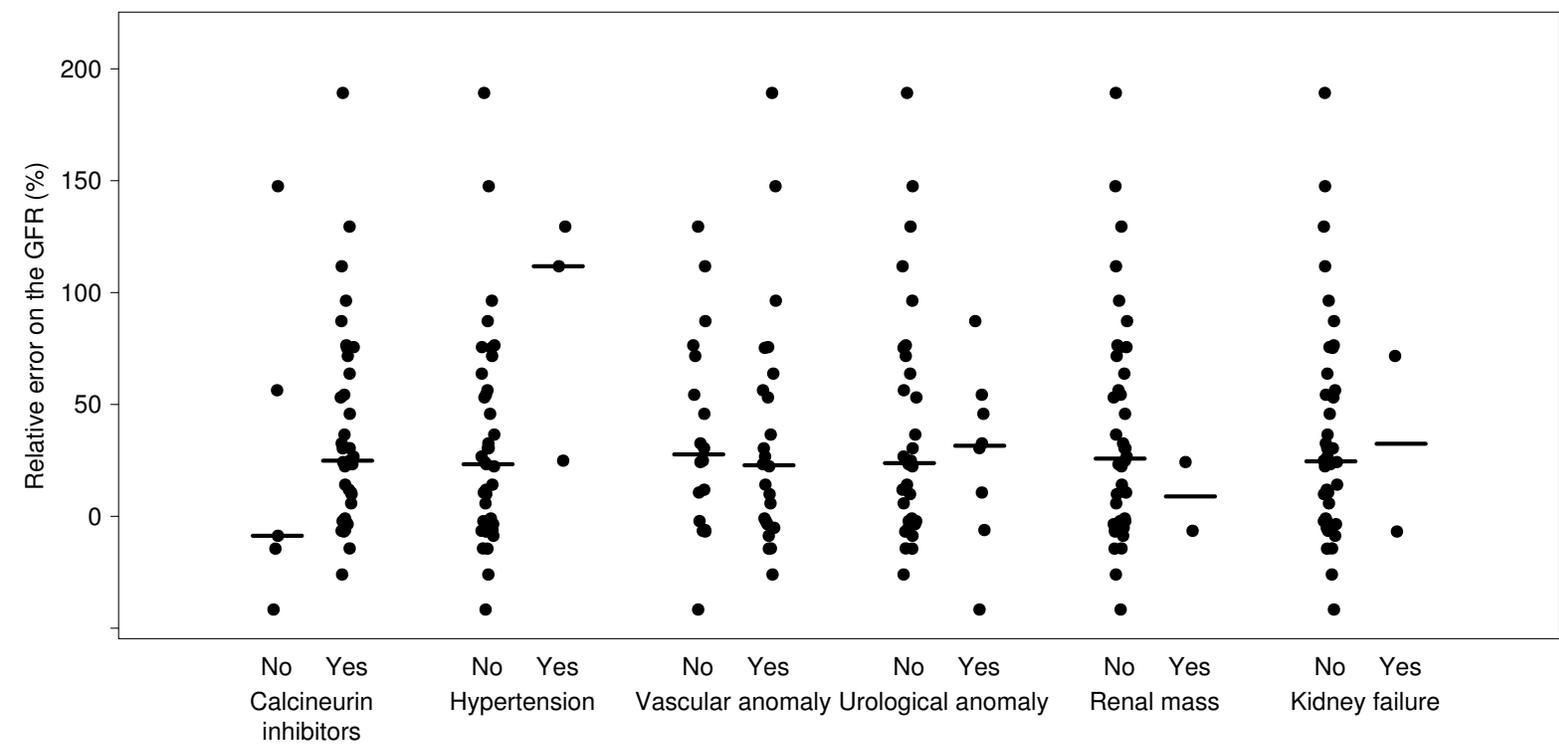


Figure 6



Supplemental material

[Click here to download Supplementary File\(s\): supplemental-material.docx](#)