Decreased renal perfusion during acute kidney injury in critical COVID-19 assessed by magnetic resonance imaging: a prospective case control study

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32
33   **Abstract**

34   **Background:** Renal hypoperfusion has been suggested to contribute to the development of

35   acute kidney injury (AKI) in critical COVID-19. However, limited data exist to support this.

36   We aim to investigate the differences in renal perfusion, oxygenation and water diffusion

37   using multiparametric magnetic resonance imaging in critically ill COVID-19 patients with

38   and without AKI.

39   **Methods**: A prospective case-control study where patients without prior kidney disease

40   treated in intensive care for respiratory failure due to COVID-19 were examined. Kidney

41   Disease: Improving Global Outcomes Creatinine criteria was used for group allocation. Main

42   comparisons were tested using Mann-Whitney U-test.

43   **Results:** Nineteen patients were examined, ten with AKI and nine without AKI. Patients with

44   AKI where examined in median 1[0-2] day after criteria fulfilment. Age and baseline Plasma-

45   Creatinine were similar in both groups. Total renal blood flow was lower in patients with AKI

46   compared with patients without (median 645 quartile range [423-753] vs. 859 [746-920]

47   ml/min, $P = 0.037$). Regional perfusion was reduced in both cortex (76 [51-112] vs. 146 [123-

48   169] ml/100g/min, $P = 0.015$) and medulla (28 [18-47] vs. 47 [38-73] ml/100g/min, $P =$

49   0.03). Renal venous saturation was similar in both groups (72% [64-75] vs. 72% [63-84], ns.),

50   as was regional oxygenation (R_2^*) in cortex (17 [16-19] vs. 17 [16-18] 1/s, ns.) and medulla

51   (29 [24-39] vs. 27 [23-29] 1/s, ns.).

52 **Conclusions:** In critically ill COVID-19 patients with AKI, the total, cortical and medullary

53 renal blood flows was reduced compared with similar patients without AKI, whereas no

54 differences in renal oxygenation were demonstrable in this setting.

55 **Trial registration:** ClinicalTrials ID: NCT02765191, registered May 6 2014 and updated

56 May 7 2020.

57

58 **Introduction**

59 Acute kidney injury (AKI) is independently associated with increased mortality in

60 hospitalized patients with corona virus disease 19 (COVID-19) and may result in higher odds

61 of death than AKI due to other causes.[1] AKI also increases the risk of impaired kidney

62 function in surviving patients after the acute phase of COVID-19.[2] A recent meta-analysis

63 of patients in intensive care units (ICUs) from several continents estimated an incidence of

64 AKI of 46%, with 19% receiving renal replacement therapy (RRT).[3]

65

66 The pathogenesis of AKI in COVID-19 has several contributing factors.[4] Since the majority

67 of critically ill COVID-19 patients who develop AKI do so within 24 hours of intubation,[5]

68 altered renal haemodynamics as a consequence of the application of a positive end-expiratory

69 pressure (PEEP) and the administration of sedative drugs with cardiovascular depressing

70 effects may contribute to the development of AKI in critically ill patients with COVID-19.

71 This is consistent with the early occurrence of severe oliguria previously reported by our

72 group.[6] Reduced renal perfusion and increased renovascular resistance have been

73 demonstrated in AKI due to non-infectious causes as well as AKI associated to sepsis.[7-9]

74 However, whether these are causative or a secondary feature of AKI is still unknown. An

75 inability to reduce kidney oxygen consumption by limiting tubular transport of sodium has

76 been associated with AKI,[7, 10] which in combination with reduced perfusion and oxygen

77 delivery result in renal hypoxia. Emerging non-invasive multiparametric magnetic resonance

78 imaging (mpMRI) techniques offer novel possibilities to investigate perfusion, oxygenation

79 and tissue characteristics in kidney disease.[11-13]

80

81 We hypothesize that AKI-development during critical COVID-19 is associated with reduced

82 renal blood flow, impaired renal oxygenation and increased renal water content. Here, we aim

83 to investigate differences in perfusion, oxygenation and water diffusion using MRI in

84 critically ill COVID-19 patients with or without AKI.

85

86 **Material and Methods**

87 *Patient cohort and study design*

88 The study was approved by the Uppsala Regional Ethical Review Agency (No. 2014/381 with

89 amendment No. 2020-01996 and No. 2021-04798). Informed consent was obtained from each

90 patient, or next of kin if the patient was unable to give consent. The Declaration of Helsinki

91 and its subsequent revisions were followed. This is a prospective case control sub-study of the

92 MR-Evaluation of Renal Function In Septic Patients (MERSEP) study, the protocol of the

93 study was pre-registered (ClinicalTrials ID: NCT02765191), first registered in May 6 2014

94 with a COVID-19 updated protocol registered May 7 2020 prior to the first patient being

95 enrolled. The study was conducted at Uppsala University Hospital, a tertiary care center in

96 Uppsala, Sweden. The main end-point comparisons were predefined as between-group

97 differences of the measures included in renal mpMRI between patients with AKI or no/low

98 grade AKI (AKI group and NO AKI group). All recruited patients that completed at least one

99 scan session are included in this paper. Due to the novelty of the mpMRI, healthy volunteer

100 data provided from an existing cohort collected at the Sir Peter Mansfield Imaging Centre,

101 Nottingham, UK with identical mpMRI sequences (approved by the Faculty of Medicine and

Health Sciences Research Ethics Committee E14032013), has been added *post-hoc* for

secondary comparison of measurements of perfusion, oxygenation, and T_1 to facilitate

interpretation.

Adult patients with polymerase chain reaction (PCR) confirmed COVID-19 and AKI or at

risk of AKI-development admitted to the ICU were screened for inclusion. Exclusion criteria

were pregnancy, preexisting end stage renal failure or dialysis, contraindications for MRI-

scanning (e.g. pacemaker or certain metal implants), deterioration or instability in vital

parameters to a degree where MRI is not feasible (e.g. dependence of prone-positioning).

Group participation in the AKI group was determined based on the Kidney Disease Improving

Global Outcome (KDIGO) creatinine criteria only[14] due to common occurrence of oliguria

without a reduction of glomerular filtration.[6] Baseline Plasma (P)-Creatinine was

determined as the lowest value within a normal range during the previous six months up to

MRI exam. Group allocation to the AKI-group was determined as fulfilment of the KDIGO

Creatinine criteria at the day of the MRI exam, or within twelve hours after the MRI exam.

All other patients were assigned as NO AKI. Measurement of P-Creatinine was made at least

every morning during ICU-stay. Group sizes of n=10 were calculated to have statistical power

$(1-\beta)$ of ≥ 0.8 and alpha coefficient ≤ 0.05 for a 20% difference in total renal blood flow and

10% in oxygenation using data from healthy volunteers.[11]

Patients were transported to the MRI scanner by dedicated ICU-staff. Mechanically ventilated

patients were ventilated with a Maquet Servo-i MR-Conditional ventilator (Getinge AB,

Sweden) during the MRI exam with the same positive end expiratory pressure (PEEP) as

before transport and fraction of inhaled oxygen (FiO_2), respiratory frequency and inspiratory

pressures adjusted to maintain target blood oxygen saturation (SpO_2) and minute ventilation.

127   Sedation regime and vasoactive treatment, when present, was continued throughout the MRI

128   exam. Saturation with pulse oximetry and invasive arterial pressure was monitored

129   continuously and recorded manually every 5 minutes. Remaining medical data and history

130   were collected from the patients' electronic medical record. Laboratory investigations were

131   performed by the Department of Clinical Chemistry as in clinical practice.

132

133   Details of the renal multiparametric MRI measures have been described in a previous

134   publication, and are summarized regarding technique and output parameter in Table 1.[15]

135   Participants were scanned on a 3T MR scanner (Achieva dStream, Philips Healthcare, Best,

136   The Netherlands) in a supine position. The MRI protocol was designed to be ~ 35-40 minutes

137   in duration, with MRI parameters guided by previous studies.[15-17] A full description of the

138   MRI acquisition and analysis can be found in Additional file 1. MRI data analysis was

139   performed blinded to AKI status. Healthy volunteers' data were taken from a previously

140   published study,[16] performed on the same field strength and vendor MR scanner (Philips 3T

141   Achieva) using identical pulse sequence parameters.

142

143   *Statistical analysis*

144   Continuous variables are expressed as median [interquartile range]. The mean of the measured

145   variable from both kidneys was used as the end point for comparison. If a measurement in a

146   single kidney was missing or unreliable, the value from the other kidney was used instead.

147   Missing data were otherwise excluded. Kruskal-Wallis one way analysis of variance was used

148   to compare the two study groups with healthy volunteers. Between-group differences of

149   continuous variables were tested using a Mann-Whitney U-test. Correlations between

150   continuous variables were calculated using Product Moment Correlation (Pearson) in

151   GraphPad Prism (version 9.3.1 for Windows, GraphPad Software, San Diego, California

152 USA, www.graphpad.com). Descriptive data were calculated using Excel 2016 (Microsoft,

153 Santa Rosa, California), and other statistical calculations were made using Statistica 13.5.0.17

154 (TIBCO Software, Palo Alto California). Graphs were made using SigmaPlot 14.0 (Systat

155 Software, San Jose, California) and Matlab (The MathWorks, Inc).

156

157 **Results**

158 *Patient Cohort*

159 Nineteen (19) patients treated in ICU for acute respiratory failure due to COVID-19 were

160 included in the study. The median age of patients was 65 [61-72] years, comparable to the

161 healthy volunteer groups' median age of 65 [58-73] years. Comorbidities were common in the

162 study cohort with COVID-19. There was a history of hypertension in 63% of patients, 32%

163 had diabetes mellitus and 68% were treated with angiotensin converting enzyme inhibitor

164 (ACEi) or angiotensin receptor blocker (ARB) before hospital admission. Dexamethasone

165 was used to treat 79% of patients to improve patient outcome in COVID-19 with similar

166 proportions between the two groups (Table 2). Acute respiratory distress syndrome (ARDS)

167 of at least moderate severity was diagnosed during the ICU stay in 95% of the patients

168 including all patients in the AKI group.

169

170 All patients had at least one measurement of P-Creatinine within normal range during the

171 current hospitalization prior to the MRI exam. In the NO AKI group, none of the patients

172 fulfilled KDIGO Creatinine criteria during the first 48 hours following the MRI exam. During

173 the following ICU-care, two patients in the AKI group received renal replacement therapy

174 (RRT). During the whole course of hospitalization 80% of patients in the AKI group and none

175 (0%) in the NO AKI group had at least one episode of severe AKI (Stage 2 or 3 according to

176 KDIGO creatinine criteria). At 90 days from inclusion, 12 patients were still alive. Patient

177 characteristics, comorbidities and outcomes are further presented group wise in Table 2.

178

179 At the time of the MRI exam (Table 3), the patients had been treated in the ICU for 4 [3-8]

180 days of which 89% required invasive ventilation for the previous 3[2-4] days. In the AKI

181 group, the KDIGO Creatinine criteria for current episode of AKI was fulfilled in median 1

182 day [0-2] prior to the exam and 2 (20%) of patients already had developed severe AKI, stage

183 2 or 3 at the time of the exam. The patients were general circulatory stable. Of the 63% of

184 patients receiving vasoactive drugs, low doses were used, one received 2 µg/kg/min of

185 dobutamine and the others received no more than 0.1 µg/kg/min noradrenaline. All patients

186 had a mean arterial pressure above 65 mmHg and all but two patients had a P-Lactate below 2

187 mmol/l. There were no adverse events recorded during the exams.

188

189 *Multiparametric MRI*

190 Not all parameters could be obtained in all subjects due to technical issues related to the

191 scanner or significant artifacts within the data. The number of valid exams are specified for

192 each mpMRI measure in Figure 1 and Table 4.

193

194 *Total renal blood flow measured by Phase Contrast. (Figure 1 a)*

195 Total renal blood flow (RBF) was lower in the AKI group compared with the NO AKI group

196 (645 mL/min [423-753] vs. 859 ml/min [746-920], p=0.037). RBF in the NO AKI group was

197 similar to that in healthy controls, 825 ml/min [720-972] (n.s.). Adjusting RBF by total kidney

198 volume attenuated the differences between groups and rendered them not statistically

199 significant (Table 4). Renal resistive index (RI) could be determined in all but one patient in

200   the NO AKI group, and was higher in the AKI group compared with the NO AKI group (0.90

201   [0.82-0.93] vs. 0.79 [0.75-0.86], p<0.046, Table 4).

202

203   *Regional renal tissue perfusion measured by ASL. (Figure 1 b, c)*

204   There were significant differences in cortical perfusion computed by ASL between the groups

205   (p<0.001). Lowest cortical perfusion was present in the AKI group at 76 ml/100g/min [51-

206   112] whilst the NO AKI group had cortical perfusion of 146 ml/100g/min [123-169]

207   (p=0.015). The cortical perfusion in the NO AKI group was lower compared with healthy

208   volounteers' 197 ml/100g/min [167-231] (p=0.009). Medullary perfusion was also reduced in

209   the AKI group compared with the NO AKI group (28 ml/100g/min [18-47] vs. 47

210   ml/100g/min [38-73], p=0.03). There was a similar proportion of regional perfusion

211   (Cortical/Medullary perfusion) in the two patient groups with ratios of 2.4 [2.2-3.3] and 2.2

212   [1.7-3.4] (n.s.) for the AKI and NO AKI groups respectively. A representative image of ASL

213   perfusion from each group is presented in Figure 2.

214

215   *Regional and global oxygenation measured by BOLD R_2* and TRUST. (Figure 1 d-f)*

216   We could not demonstrate any differences between the groups in either cortical or medullary

217   oxygenation (Fig 1 d, e). Cortical R_2* was 17 (1/s) [16-19] in the AKI group and 17 (1/s) [16-

218   18] in the NO AKI group. In the renal medulla, R_2* was 29 (1/s) [24-39] in patients with AKI

219   compared with 27 (1/s) [23-29] in patients with NO AKI. R_2* values were similar to healthy

220   volunteers' (Fig 1 d, e). Left renal venous saturation assessed with TRUST was also similar

221   between the AKI and the NO AKI groups (72% [64-75] vs. 72% [63-84], ns.) with large

222   variations within groups (Fig 1 f).

223

224   *Regional tissue composition and water diffusion.*

225 Cortical and medullary ADC, D, D* or f_p, and tissue composition (cortical T_1 and T_2 and

226 medullary T_1) did not differ between the AKI and NO AKI groups (Table 4). Cortical T_1 was

227 longer in the AKI group (1560 ms [1524-1638]) compared with healthy volunteers (1459 ms

228 [1400-1525], p= 0.009).

229

230 *Post hoc analyses*

231 Correlations were made *post hoc* using the entire study population with COVID-19 examining

232 relations between physiologic parameters and perfusion, as well as imaging data affected by

233 changes in water content. This was performed explore physiological factors which may

234 affects renal perfusion and to facilitate the interpretation of the regional oxygenation data.

235 Correlations are summarized in matrices in Figure 3.

236

237 **Discussion**

238 The main findings in this study are that in critically ill COVID-19 patients with AKI, the total,

239 cortical and medullary renal blood flows are reduced compared with patients without AKI, as

240 assessed by magnetic resonance imaging. There were no demonstrable differences in regional

241 or global renal oxygenation, tissue composition or water diffusion. The findings are consistent

242 with the hypothesis that impaired renal blood flow contributes to AKI in COVID-19.

243

244 Our observations of reduced renal perfusion during AKI in COVID-19 are in line with prior

245 observations in AKI due to bacterial septic shock,[7, 9] and thoracic surgery.[10] Results of

246 renal ultrasound in critical COVID-19 have also implied reduced perfusion either using

247 contrast enhancement or as an indirect observation of larger values of resistance index.[18,

248 19] We also show increased resistive index correlated with lower total renal blood flow.

249 Multiparametric MRI has previously been used in a study of nine patients with severe AKI of

250   different etiologies at a median of six days after peak P-Creatinine, also demonstrating a

251   reduced renal perfusion.[17] In our study, differences in renal perfusion between groups were

252   partly attenuated after adjusting for total kidney volume (TKV). Reduced TKV (because of

253   loss of functional mass) predisposes for AKI development while AKI development in itself

254   increases TKV. [17] Although we could not demonstrate significant differences in TKV

255   between the groups, adjustment may have introduced more uncertainty to the data by these

256   mechanisms.

257   A limitation to the above-mentioned studies using thermodilutional catheters[7, 10] or phase

258   contrast MRI[9] to determine total renal blood flow is that regional hypoperfusion cannot be

259   investigated. Using ASL MRI in this study, we additionally demonstrate reduced regional

260   perfusion in both renal cortex and medulla.

261

262   Dehydration and reduced circulating blood volume resulting in hypoperfusion of the medulla

263   is a well-known mechanism of AKI,[20] and has been suggested as a major contributor to

264   AKI development in severe COVID-19.[21] However, the evident systemic inflammation

265   with increased levels of cytokines in critical COVID-19[22] is also associated with AKI

266   development.[23] In animal experiments, systemic inflammation can cause AKI with normal

267   kidney perfusion and even with hyperperfusion.[24, 25] As mean arterial pressure did not

268   correlate with changes in regional perfusion in our study, renal autoregulation may still partly

269   attenuate the consequences of hypoperfusion during normotensive conditions during critical

270   COVID-19.

271

272   We find a discrepancy in the renal perfusion in our study when evaluated using phase

273   contrast-MRI compared to ASL, however a strong correlation between values was shown

274   (Figure 3). Total perfusion assessed with PC-MRI was not indexed for renal or body size

275   whereas regional perfusion is expressed per 100g functional tissue. Since the median TKV in

276   both groups were similar, the relative difference between groups would be expected to be

277   similar if the modalities were interchangeable. PC-MRI is sensitive to errors in planning the

278   angle whereas ASL-estimates depend on cortical mapping where inclusion of low-perfused

279   areas in voxels reduce the estimated mean. RBF determined by phase contrast has a higher

280   intra-individual variability than cortical ASL.[15] A similar discrepancy between perfusion

281   between PC-MRI and ASL has been found in a previous study of CKD where the reduction in

282   perfusion compared to healthy individuals was more pronounced using ASL compared to PC-

283   MRI.[15] Therefore, values of these two modalities are not interchangeable, at least not

284   during pathological conditions, and have qualitative differences. Taken together they

285   nonetheless strengthen the interpretation that renal perfusion is reduced early during AKI in

286   ICU-patients with COVID-19.

287

288   Despite a marked reduction in regional perfusion in both cortex and medulla we could not

289   reveal differences in renal oxygenation in patients with AKI compared with those without,

290   using either BOLD or TRUST sequences. In fact, BOLD imaging rather demonstrates the

291   same level of renal oxygenation as healthy individuals of similar age. This is also similar to

292   the findings when AKI patients were investigated 6 days after peak P-Creatinine.[17] A

293   strength of TRUST is its insensitivity to haemodilution and edema. Renal venous saturation

294   using TRUST in healthy volunteers has been estimated to 89±2% by our group (unpublished

295   data) which is close to values expected from measurements with renal vein catheters but

296   differs from our study population.[7] As such, the TRUST-values here imply increased renal

297   oxygen extraction in COVID-19 patients in general.

298

299 Our results do not support hypoperfusion-induced renal hypoxia as a specific feature of early

300 AKI in COVID-19. Possible explanations as to how reduced perfusion in both medulla and

301 cortex is not accompanied by detectable renal hypoxia include offsets in the relation between

302 tpO_2 and the BOLD signal during COVID-19 associated AKI. The BOLD signal is generated

303 by the occurrence of deoxyhaemoglobin, with a linear relationship between intrarenal

304 deoxyhaemoglobin content and R_2^*.[26] Increased water content decreases both R_2 and R_2^*

305 strongly and differences therein may attenuate differences in deoxyhaemoglobin content.

306 Influence of water content is supported by the correlations between R_2^*, R_2, T_1, and ADC in

307 the patient group (Figure 3). Further, intrarenal microthrombotization have also been

308 demonstrated in COVID-19 associated AKI and may contribute to increased renal

309 resistance.[4, 27] Since thrombotized vessels only transitorily contain deoxyhaemoglobin the

310 effect on BOLD-signal may not be detectable. Also, decreased intrarenal blood volume due to

311 vasoconstriction or changes in oxygen transit in tissue could also offset the relation between

312 tPO_2 and renal oxygenation measured using BOLD.[28] We cannot conclude if these

313 mechanisms contribute to our findings or to what extent.

314

315 Tissue composition and DWI parameters did not differ between the two patient groups but T_1

316 values differed from healthy controls. We are unable to conclude if these findings are due to

317 COVID-19 or caused by comorbidities. Previous investigations of patients with CKD found

318 both lower ADC and longer T_1 compared with healthy controls.[16] However, longer T_1 is

319 also found in the acute phase of AKI with a reduction to healthy population's mean after a

320 year of recovery accompanied with a reduction to normal of total kidney volume.[17] The

321 higher T_1 values may thus reflect higher water content in inflammatory, edematous tissue.

322

323   Both the early investigation and a comparator group of COVID-19 patients treated in the ICU

324   without AKI adds substance to the observations presented. Some limitations related to the

325   MRI sequences have been addressed previously. Further limitations include that TRUST is a

326   more novel sequence in renal MRI where pitfalls in the renal application is less explored. In

327   our study there were also more missing values due technical problems with this sequence and

328   a larger variation in range of estimates in the TRUST measurements compared with BOLD.

329   The COVID-19 cohort and the healthy volunteers imaging data were acquired on a different

330   scanner, but importantly this used the same sequences and we have reported similar measures

331   between the two scanners in young healthy volunteers.[11, 15] As the main comparison is

332   between patients with AKI and NO AKI with COVID-19 we do not consider this a major

333   limitation. Relatively few patients have been included in both groups all from a single center.

334   Patients in the AKI and the NO AKI differ besides renal function as patients in the AKI group

335   were treated longer in the ICU, with higher proportion of IMV and with higher PEEP. We

336   could not find a significant correlation between PEEP during the MRI exam and global or

337   regional renal perfusion, but are unable to draw further conclusions regarding the influence of

338   respiratory therapies. There is a skewness in the study population compared with ICU-

339   populations with COVID-19 at large, since severely deteriorated patients where MRI was not

340   feasible were excluded. Still, in our opinion, the disease severity of the cohort represent a

341   relevant part of the patients in the ICU and the timing of the MRI exam in relation to the

342   course of the disease represents a phase where therapeutic interventions are much needed.

343

344   **Conclusion**

345   By using novel state-of-the-art techniques this study demonstrates that in critically ill patients

346   with COVID-19, patients with AKI have decreased total, cortical and medullary renal blood

347   flow without effects on renal oxygenation compared with patients without AKI.

348 **List of abbreviations**

349 ACEi – angiotensin converting enzyme inhibitor

350 ADC - apparent diffusion coefficient

351 AKI – Acute Kidney Injury

352 ARB - angiotensin II receptor blocking drug

353 ARDS – acute respiratory distress syndrome

354 ASL - Arterial Spin Labelling

355 BOLD - Blood Oxygen Level Dependent

356 CKD – chronic kidney disease

357 COPD – chronic obstructive pulmonary disease

358 CRP – C-reactive protein

359 D - pure diffusion

360 D*- pseudodiffusion

361 DWI – Diffusion Weighted Imaging

362 eGFR – estimated glomerular filtration rate

363 eFF – estimated filtration fraction

364 *Fp* - perfusion fraction

365 ICU – Intensive Care Unit

366 IMV – invasive mechanical ventilation

367 IQR – interquartile range

368 KDIGO - Kidney Disease Improving Global Outcome

369 MAP - Mean arterial pressure

370 mpMRI – multiparametric Magnetic Resonance Imaging

371 NT-proBNP – N-terminal pro-brain natriuretic peptide

372 PEEP – positive end expiratory pressure

373   P/f – PaO_2/FiO_2

374   PC - Phase Contrast

375   R_2^* - BOLD relaxation rate

376   RBF – Renal Blood Flow

377   RRT – Renal Replacement Therapy

378   SAPS 3 - Simplified Acute Physiology Score 3

379   SOFA - Sequential Organ Failure Assessment

380   T_1 – longitudinal relaxation time.

381   T_2 – transverse relaxation time

382   TRUST - T_2 Relaxation Under Spin Tagging

383

384   **Declarations**

385   *Ethics approval and consent to participate*

386   The study was approved by the Uppsala Regional Ethical Review Agency (No. 2014/381 with

387   amendment No. 2020-01996 and No. 2021-04798). Informed consent was obtained from each

388   patient, or next of kin if the patient was unable to give consent. The Declaration of Helsinki

389   and its subsequent revisions were followed. This is a prospective case control sub-study of the

390   MR-Evaluation of Renal Function In Septic Patients (MERSEP) study, the protocol of the

391   study was pre-registered (ClinicalTrials ID: NCT02765191), first registered May 6 2014 with

392   a COVID-19 updated protocol registered May 7 2020 before first patient was enrolled.

393

394   *Data availability*

395   The datasets generated and/or analysed during the current study are not publicly available due

396   national and EU regulations regarding patient related data, but are available from the

397   corresponding author on reasonable request.

Authors' contributions

TL, PE, SF, JW, FP, ML, PL and RF contributed to conception and design of the study. TL, RF, SBA, ML, FTM and MH, acquired physiological data and managed patient participation and safety. TL collected clinical patient data. SF provided imaging protocol. PE, JW and PL performed imaging. EC and SF performed imaging analyses. TL, PE, EC, SF, MH, and RF performed data analysis and curation. The first draft of the manuscript was written by TL. TL and EC prepared images. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript for publication.

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525   "Additional file 1.doc" contains:

526   1.   Description of MRI data acquisition and Analysis

527   2.   Scatterplots with correlation-lines and 95% confidence intervals of predicted mean of

528   selected parameters from Figure 3.

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534   **Table 1.** *Description of multiparametric renal MRI measures.*

Name: Phase Contrast (PC) Category: Global perfusion Output: Total renal blood flow (ml/min)	Measurement of blood flow in renal arteries and veins. Sensitized to flow by using bipolar gradients affecting the phase signal of spins that flow with a uniform velocity in the direction parallel to the gradients. By utilizing ECG gating, blood velocity and vessel area is measured across 15- 20 points in the cardiac cycle during a breath hold of approximately 15-20 s. Global perfusion of the kidney can be measured by dividing total blood flow to the kidney by the total kidney volume (TKV). Causes of systematic falsely low estimations of blood flow include: non-perpendicular placement of the imaging plane, inaccurate estimation of elastic dilatation of the artery during cardiac cycle, aberrant arteries or placement of field down stream of arterial bifurcations. Intra-individual coefficient of variation is quoted to be 14%.
Name: Arterial Spin Labelling (ASL) Category: Regional perfusion Output: Regional perfusion Cortex and Medulla (ml/100g/min)	A subtraction technique where arterial blood water is labelled (inverted) prior to imaging. Difference signals are determined by subtracting imaging data with and without labelling. Data is collected using respiratory triggering. The resulting ASL difference images are dependent on tissue perfusion, with regional perfusion in the cortex and medulla calculated from a kinetic model. A Gaussian fit to all voxels within the perfusion maps in cortex and medulla masks is performed. Edema may introduce bias as blood:tissue coefficient is assumed constant. Intra-individual coefficient of variation is 9%.

Name:	Deoxyhaemoglobin is paramagnetic and shortens the transverse relaxation constant T_2^* (ms) which is the inverse of the relaxation rate R_2^* (1/s). Images are collected during a breath hold of approximately 15-20s. Besides oxygenation, R_2^* is also influenced by changes in hematocrit and tissue water content. Increased water content prolongs both T_2 and T_2^* (and shortens R_2^*) relaxation times. Intra-individual coefficient of variation in R_2^* is 4%.
Blood Oxygen Level Dependent (BOLD)	
Category:	
Regional oxygenation	
Output:	
R_2^*(relative measure of oxygenation)	
Name:	Spin tagging of blood, similar to ASL, is used to separate the signals from venous blood from surrounding tissues, and this is collected across a range of T_2-weighted echo times. By acquiring an R_2 signal solely from venous blood the venous oxygenation (saturation) can be calculated. In contrast to BOLD, TRUST data is not influenced by edema and hematocrit. Renal TRUST is a novel technique with limited previous data and is less explored compared with BOLD. Validation studies are mainly from the central nervous system to study the sagittal sinus.
T_2 Relaxation Under Spin Tagging (TRUST)	
Category:	
Global oxygenation	
Output:	
Renal venous saturation (%)	
Name:	DWI determines signals from the Brownian motion of water in tissue by acquiring data at a range of b-values which alters the measured apparent diffusion coefficient (ADC). ADC is increased in the presence of oedema. Incorporation of the IntraVoxel Incoherent Motion (IVIM) bi-exponential model is used to calculate the pure diffusion of water in tissue coefficient (D) separated from pseudodiffusion (D*) representing microscopic intravoxel flows of blood or urine, and the perfusion fraction f_p (%). Intra-individual coefficient of variation of ADC is typically 3%, whilst those of D, D* and f are 9, 39, 22%.
Diffusion weighted imaging (DWI)	
Category:	
Regional water diffusion	
Output:	
Apparent diffusion coefficient (ADC), D, D*, f_p.	
Name:	Structural imaging and relaxation time mapping. Signal intensity and contrast between tissues can be manipulated by repetition time and echo time of the measurement sequences. A strongly T2-weighted sequence allows total kidney volume (TKV) to be measured. Absolute values of tissue relaxation times differ between 1.5T and 3T scanners. T_1 mapping in this study is performed using a respiratory triggering inversion recovery technique, with a curve fitting function used to obtain a T_1 value. T_2 mapping is performed using a respiratory triggered GRASE scheme. Intra-individual coefficient of variation in T_1-mapping is 2% whereas intra-individual coefficient of variation of TKV is 4%.
T_2-weighted imaging, and T_1 and T_2 mapping	
Category:	
Structure	
Output:	
Total kidney volume (TKV), T_1 and T_2 relaxation times	

535   Outline of multiparametric renal MRI measures collected in the study divided into different

536   categories, as detailed in a previous published description.[15]

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541   **Table 2.** *Patient characteristics, comorbidities and outcome*

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	AKI (N=10)	NO AKI (N=9)
Age, years [IQR]	66[64-72]	65 [53-70]
Male, n (%)	8 (80%)	8 (89%)
Height, cm [IQR]	173 [169-177]	180 [170-187]
Weight, kg [IQR]	94 [82-102]	86 [80-102]
Body Mass Index, [IQR]	32 [27-35]	27 [26-36]
Hypertension, n (%)	7 (70%)	5 (56%)
History of treatment with ARB/ACEi, n (%)	7 (70%)	6 (67%)
Diabetes, n (%)	4 (40%)	2 (22%)

Ischemic heart disease or congestive heart failure, n (%)	3 (30%)	2 (22%)
Ischemic heart disease, n (%)	3 (30%)	1 (11%)
Congestive heart failure, n (%)	0 (0%)	1 (11%)
Asthma or COPD, n (%)	2 (20%)	0 (0%)
History of CKD, n (%)	0 (0%)	0 (0%)
Baseline Plasma-Creatinine, μmol/l [IQR]	68 [65-77]	66 [58-73]
Most severe AKI-stage during hospital stay, [IQR]	2[2-3]	0[0-1]
AKI stage 2 or 3 any time during hospital stay, n (%)	8 (80%)	0 (0%)
RRT at any time in ICU, n (%)	2 (20%)	0 (0%)
SAPS 3, [IQR]	54[52-56]	53[50-55]
Days of symptomatic COVID-19 at ICU-admission, [IQR]	9[8-11]	9[9-10]
Treatment with dexametasone, n (%)	8 (80%)	7 (78%)
IMV at any time during ICU stay, n (%)	10 (100%)	7 (78%)
Days with IMV, [IQR]	18[15-22]	14[6-18]
Vasoactive treatment at any time in ICU, n (%)	10 (100%)	7 (78%)
Moderate or severe ARDS, n (%)	10 (100%)	8 (89%)
Severe ARDS, n (%)	8 (80%)	5 (56%)
90-day survival, n (%)	6 (60%)	6 (67%)

543 Patient characteristics, comorbidities and outcome in the 19 patients treated in ICU for

544 respiratory failure due to COVID-19 included in study.

545 Abbreviations; IQR – interquartile range, ARB - angiotensin II receptor blocking drug, ACEi – angiotensin

546 converting enzyme inhibitor, COPD – chronic obstructive pulmonary disease, CKD – chronic kidney disease, AKI

547 – acute kidney injury, RRT – renal replacement therapy, ICU – intensive care unit, SAPS 3 - Simplified Acute

548 Physiology Score 3, IMV – invasive mechanical ventilation, ARDS – acute respiratory distress syndrome.

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551   **Table 3.** *Patient characteristics of physiologic parameters at MRI exam*

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	AKI (N=10)	NO AKI (N=9)
Current Plasma-Creatinine, μmol/l [IQR]	104[101-114]	67 [64-77]
Current eGFR (Creatinine), ml/min [IQR]	56[49-59]	87 [78-90]
Current KDIGO Creatinine AKI Stage	1[1-1]	
Last recorded hourly urine output, ml/kg [IQR]	0.9[0.3-1.7]	1 [0.8-1.7]
Last recorded hourly urine output, ml [IQR]	65[35-131]	110 [80-150]
Furosemide within 12 hours before MRI scan, mg [IQR]	8[1-10]	0 [0-0]
Time since latest furosemide, h [IQR]	7[5-20]	28 [17-36]
Any furosemide within 3 hours before MRI scan, n (%)	2 (20 %)	1 (11 %)
Net fluid intake at exam day, ml [IQR]	318[-15-629]	184 [-16-429]
SOFA score, points [IQR]	7[7-8]	6 [4-6]
Days of symptomatic COVID-19, n [IQR]	17 [14-19]	12 [11-14]
Days in ICU at exam, n [IQR]	8 [4-8]	3 [2-5]
Plasma-CRP, mg/l [IQR]	98[71-140]	115 [64-186]
Days since start of invasive ventilation, n [IQR]	4 [2-5]	2 [2-3]
Arterial oxygen saturation	96 % [93-97]	95 % [95-98]
Arterial pO_2, kPa [IQR]	10 [10-11]	10 [10-12]
Arterial pCO_2, kPa [IQR]	6.3 [5.7–6.6]	5.5 [5.2-6]
Arterial pH, [IQR]	7.39 [7.37–7.41]	7.42 [7.4–7.44]
P/f-ratio, kPa [IQR]	21 [20-27]	26 [25-33]
PEEP, cmH_2O [IQR]	14 [13-15]	10 [9-12]
Mean arterial pressure, mmHg [IQR]	80 [79-85]	81 [80-98]
Sinus rhythm, n (%)	10 (100 %)	8 (89 %)
Blood haemoglobin, g/dl [IQR]	11.5 [11.3–12.3]	12.8 [11.4–12.9]
Central venous saturation, [IQR]	73 % [72-77]	67 % [65-74]
Vasoactive drug, n (%)	8 (80 %)	4 (44 %)
Noradrenaline dose, μg/kg/min [IQR]	0.05 [0.01-0.07]	0 [0-0.03]
Plasma-lactate, mmol/l [IQR]	1.4 [1-1.9]	1.5 [1.3–1.6]
Plasma-NT-proBNP, ng/l [IQR]	201 [131-633]	373 [236-491]

553   Patient characteristics of physiologic parameters on the day of the MRI exam in the 19 patients

554   included in the study who were treated in ICU for respiratory failure due to COVID-19.

555   Abbreviations; IQR – interquartile range, eGFR – estimated glomerular filtration rate, SOFA - Sequential Organ

556   Failure Assessment, CRP – C-reactive protein, P/f – PaO_2/FiO_2, PEEP – positive end expiratory pressure, NT-

557   proBNP – N-terminal pro-brain natriuretic peptide.

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Table 4. *Additional results of renal multiparametric MRI*

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	AKI	*n*	NO AKI	*n*	HEALTHY VOLUNTEERS	*n*
Perfusion						
Global perfusion (ml/100g/min)	168 [142-216]	10	202 [174-235]	9	220 [174-242]	12
Regional Perfusion Ratio (Cortex/Medulla)	2.4 [2.2–3.3]	10	2.2 [1.7–3.4]	7		
Resistance Index *	0.90 [0.82-0.93]	10	0.79 [0.75-0.86]	8		
Structure and regional water diffusion						
Total kidney volume (ml)	356 [331-437]	10	390 [359-447]	9	403 [345-430]	12
T_1 cortex (ms) †	1560 [1524-1638]	8	1522 [1497-1638]	8	1459 [1400-1525]	12
T_1 medulla (ms)	1838 [1732-1872]	8	1792 [1695-1870]	8	1732 [1661-1850]	12
T_2 cortex (ms)	120 [113-134]	8	124 [119-141]	8		
DWI Cortex ADC ($x10^{-3}$ mm^2/s)	1.9 [1.9–2.1]	8	2.1 [1.9–2.1]	8		
DWI Medulla ADC ($x10^{-3}$ mm^2/s)	1.9 [1.9–2.0]	8	2.1 [1.8–2.1]	8		
DWI Cortex D ($x10^{-3}$ mm^2/s)	1.8 [1.7–1.9]	8	1.9 [1.7-2]	8		
DWI Cortex D* ($x10^{-3}$ mm^2/s)	26 [23-29]	8	27 [24-28]	8		
DWI Cortex F_P	0.13 [0.11-0.15]	8	0.13 [0.11-0.14]	8		
DWI Medulla D ($x10^{-3}$ mm^2/s)	1.8 [1.7- 1.9]	8	1.9 [1.7-2]	8		
DWI Medulla D* ($x10^{-3}$ mm^2/s)	26 [23-17]	8	27 [26-28]	8		
DWI Medulla F_P	0.14 [0.11-0.17]	8	0.15 [0.12-0.16]	8		

Results of renal multiparametric MRI in 19 patients treated in ICU for respiratory failure due to COVID-19 with AKI or NO AKI, and 12 healthy volunteers of similar age. Data presented as median [quartile range]. Significant differences from Mann-Whitney U-Test between AKI and NO AKI groups are indicated by * if $P < 0.05$. Significant differences from one way Kruskal-Wallis ANOVA between all groups are indicated by † if $P < 0.05$ and ††† if $P < 0.001$. Valid numbers of MRI exams are specified for each measure and group. Additional results are presented in Figure 1.

Abbreviations; T_1 – longitudinal relaxation time, T_2 – transverse relaxation time, DWI – Diffusion Weighted Imaging, ADC – Apparent diffusion coefficient, D - pure diffusion, D*- pseudodiffusion, *Fp* - perfusion fraction

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Figure 1. *Main results of renal multiparametric MRI*

Box- and scatterplots of renal multiparametric MRI in 19 patients treated in ICU for respiratory failure due to COVID-19 with AKI and NO AKI, along with 12 healthy volunteers of similar age. Valid numbers of MRI exams are specified for each parameter and group. *P*-values from Kruskal-Wallis ANOVA. *, **, *** signifies $P < 0.05$, 0.01 and 0.001 in Mann-Whitney U test. TRUST is short for T_2 Relaxation Under Spin Tagging.

Figure 2. *Example of imaging data*

Representative regional perfusion using arterial spin labelling with perfusion maps colourized voxelwise showing representative AKI and NO AKI scans from the group of 19 patients with COVID-19 with and without AKI treated in ICU due to respiratory failure. Individual mean cortex perfusion across both kidneys are provided below each image after voxelwise Gaussian fit in each kidney to the histogram of cortical values.

Figure 3. *Post hoc correlation matrix*

Post hoc correlation matrix for combined patient groups of clinical factors (MAP, eFF and eGFR) and multi-parametric MRI measures showing absolute correlation (R) and the associated significance (*P*). eFF calculated as $eGFR_{Creatinine}/(TRBF_{Phase\ Contrast}\times(1-Hematocrit))$. Selected significant correlations of clinical factors and multi-parametric MRI measures are shown in Supplemental file.

Abbreviations; MAP - Mean arterial pressure, PEEP – positive end expiratory pressure, eFF – estimated filtration fraction, eGFR – estimated glomerular filtration rate, R_2* - BOLD relaxation rate, ADC - apparent diffusion coefficient, T_2 – transverse relaxation time, T_1 – longitudinal relaxation time, TRBF – Totalt Renal Blood Flow.

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