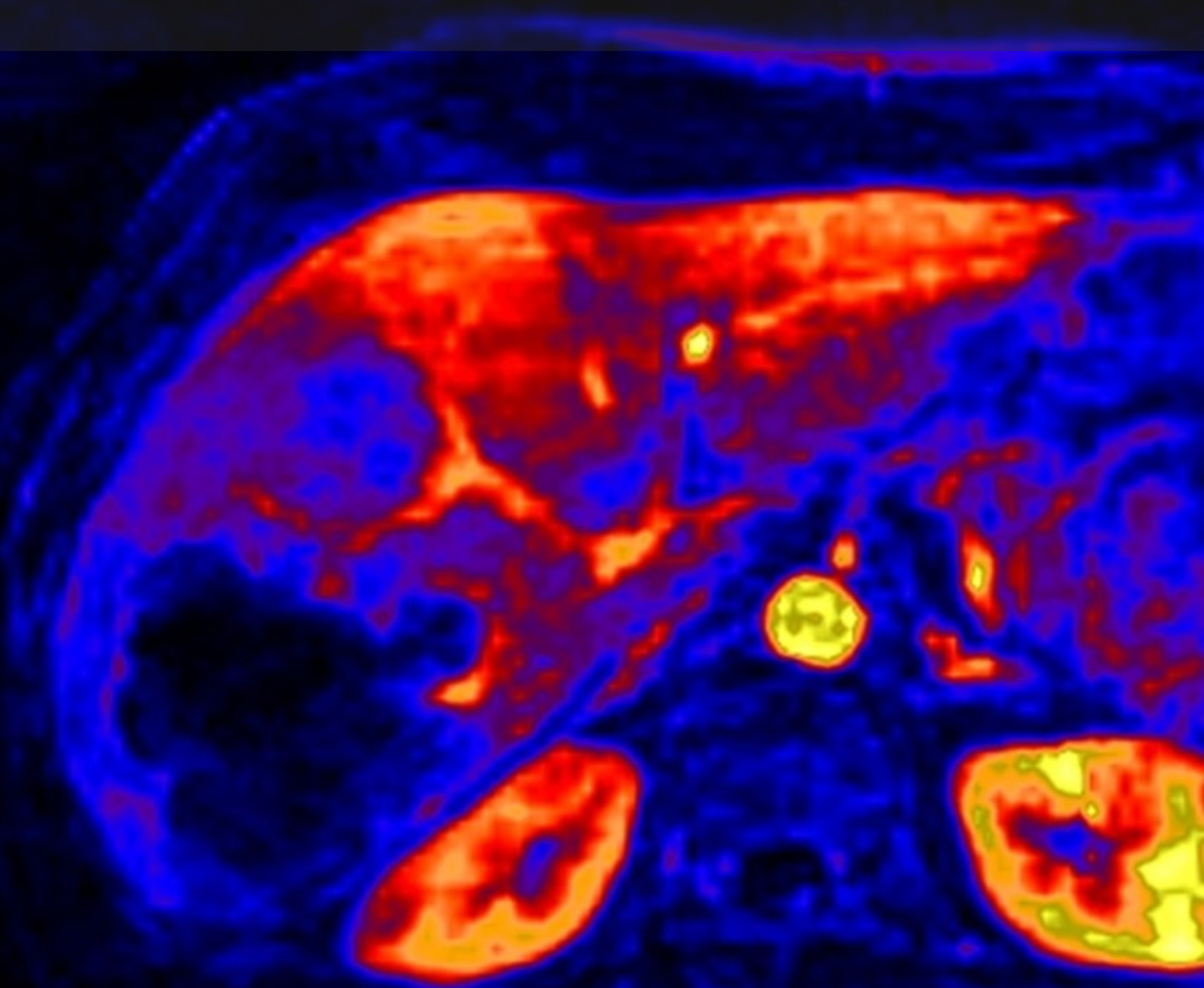


Sheffield two-compound study

ciclosporin (all results)

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Sheffield two-compound study

ciclosporin (all results)

by

miblab.org

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Two-scan results

1.1. Data summary

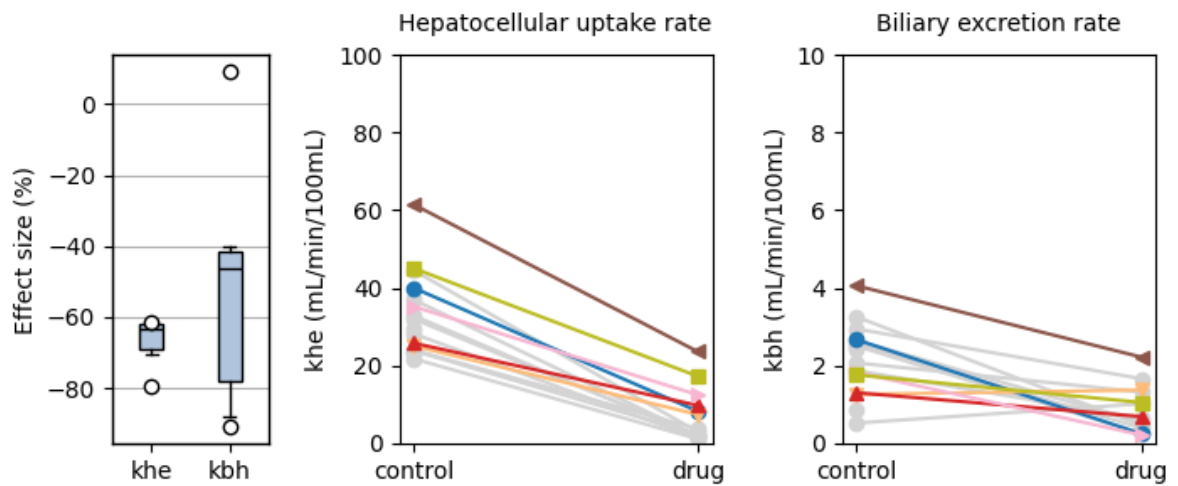


Figure 1.1: Effect size (%) on hepatocellular uptake (k_{he} , left) and biliary excretion (k_{bh} , right) of gadoxetate. The boxplot shows median, interquartile range and 95 percent range. The line plots show individual values for hepatocellular uptake (k_{he} , middle) and biliary excretion (k_{bh} , right) of gadoxetate of the control (left of plot) and treatment (right of plot). Grey lines are healthy controls with rifampicin injection.

parameter	count	mean	std	min	25%	50%	75%	max
khe effect size (%)	6.0	-66.6	7.1	-79.3	-68.9	-63.3	-61.8	-61.6
khe control (mL/min/100cm ³)	6.0	38.79	13.6	25.08	28.17	37.63	43.82	61.49
khe drug (mL/min/100cm ³)	6.0	13.14	6.24	7.43	8.65	11.13	16.06	23.61
kbh effect size (%)	6.0	-50.4	36.6	-90.6	-77.8	-46.1	-41.5	8.9
kbh control (mL/min/100cm ³)	6.0	2.15	1.06	1.26	1.42	1.8	2.46	4.06
kbh drug (mL/min/100cm ³)	6.0	0.97	0.76	0.22	0.36	0.87	1.29	2.22

Table 1.1: Effect size and absolute values of hepatocellular uptake (k_{he}) and biliary excretion (k_{bh}) of gadoxetate

1.2. Liver biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for CI (0-35min)	0.00081	47.12	131.03
AUC for CI (0-inf)	0.03317	2.82	10.52
Biliary excretion rate	0.02706	3.28	10.08
Biliary tissue excretion rate	0.05359	1.99	6.11
Extracellular dispersion	0.68617	0.4	1.26
Extracellular mean transit time	0.10081	1.26	0.14
Final biliary excretion rate	0.12814	1.07	2.92
Final hepatocellular uptake rate	0.00134	31.9	21.05
Hematocrit			
Hepatocellular mean transit time	0.12079	1.11	0.13
Hepatocellular tissue uptake rate	0.01588	4.88	33.04
Hepatocellular uptake rate	0.00069	53.2	81.22
Initial biliary excretion rate	0.02921	3.1	10.41
Initial hepatocellular uptake rate	0.00129	32.81	212.36
Liver T1-MOLLI at 45min	0.03842	2.53	0.07
Liver T1-MOLLI at baseline	0.27107	0.65	0.53
Liver T1-MOLLI at scan 2	0.97133	0.37	1.04
Liver blood clearance	0.01825	4.4	9.21
Liver extracellular volume fraction	0.26889	0.66	0.18
RE for R1l at 20min	0.00166	27.13	234.95
RE for Sl at 20min	0.00028	108.15	948.62

Table 1.2: Results of a pairwise comparison testing for differences in liver biomarkers between control and treatment. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for CI (0-35min)	mM*sec	196.0 (42.0)	86.0 (20.0)	-55.7 (7.6)
AUC for CI (0-inf)	mM*sec	706.0 (120.0)	460.0 (180.0)	-35.5 (22.0)
Biliary excretion rate	mL/min/100cm3	2.15 (0.85)	0.968 (0.61)	-50.4 (29.0)
Biliary tissue excretion rate	mL/min/100cm3	2.67 (1.0)	1.4 (1.0)	-44.8 (30.0)
Extracellular dispersion	%	76.1 (13.0)	74.3 (9.3)	-0.755 (12.0)
Extracellular mean transit time	sec	23.9 (4.0)	32.3 (7.8)	38.2 (38.0)
Final biliary excretion rate	mL/min/100cm3	2.25 (0.78)	1.7 (0.71)	-24.4 (27.0)
Final hepatocellular uptake rate	mL/min/100cm3	40.1 (12.0)	19.9 (6.9)	-50.8 (7.9)
Hematocrit	%	45.0 (0.0)	45.0 (0.0)	0.0 (0.0)
Hepatocellular mean transit time	min	44.1 (14.0)	155.0 (110.0)	319.0 (370.0)
Hepatocellular tissue uptake rate	mL/min/100cm3	217.0 (98.0)	49.0 (7.4)	-73.9 (6.1)
Hepatocellular uptake rate	mL/min/100cm3	38.8 (11.0)	13.1 (5.0)	-66.6 (5.7)
Initial biliary excretion rate	mL/min/100cm3	2.11 (0.93)	0.866 (0.57)	-52.8 (31.0)
Initial hepatocellular uptake rate	mL/min/100cm3	37.5 (11.0)	6.42 (3.1)	-83.1 (4.6)
Liver T1-MOLLI at 45min	sec	0.469 (0.1)	0.629 (0.075)	40.3 (25.0)
Liver T1-MOLLI at baseline	sec	0.734 (0.048)	0.751 (0.028)	2.68 (4.0)
Liver T1-MOLLI at scan 2	sec	0.625 (0.055)	0.623 (0.059)	0.818 (13.0)
Liver blood clearance	L/min	0.319 (0.17)	0.125 (0.061)	-54.6 (18.0)
Liver extracellular volume fraction	mL/100cm3	19.6 (4.0)	25.8 (6.3)	46.0 (63.0)
RE for R1l at 20min	%	76.0 (19.0)	24.4 (5.0)	-66.8 (7.1)
RE for Sl at 20min	%	65.8 (12.0)	22.3 (3.7)	-65.7 (3.6)

Table 1.3: Mean values along with their 95 percent confidence intervals for all liver biomarkers of the control and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

1.3. Systemic biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for Cb (0-35min)	0.10244	1.25	0.25
AUC for Cb (0-inf)	0.0801	1.49	0.15
Body extraction fraction	0.43172	0.5	1.8
Cardiac output	0.19784	0.8	2.74
Heart-lung dispersion	0.26484	0.66	3.19
Heart-lung mean transit time	0.0332	2.82	0.04
Organs blood mean transit time	0.6258	0.42	0.5
Organs extraction fraction	0.10065	1.26	0.18
Organs extravascular mean transit time	0.29915	0.61	3.03
RE for R1b at 20min	0.01026	6.77	0.07
RE for Sb at 20min	0.32668	0.58	0.27

Table 1.4: Results of a pairwise comparison testing for differences in systemic biomarkers between control and treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	30.8 (5.9)	42.2 (16.0)	33.5 (27.0)
AUC for Cb (0-inf)	mM*sec	49.3 (8.7)	77.7 (29.0)	56.3 (45.0)
Body extraction fraction	%	4.44 (0.88)	4.0 (1.3)	-9.97 (29.0)
Cardiac output	L/min	9.69 (2.1)	7.86 (3.1)	-19.0 (25.0)
Heart-lung dispersion	%	57.8 (18.0)	47.2 (6.5)	-7.61 (29.0)
Heart-lung mean transit time	sec	11.1 (1.5)	19.0 (4.6)	76.6 (56.0)
Organs blood mean transit time	sec	26.1 (5.7)	28.4 (3.4)	19.5 (43.0)
Organs extraction fraction	%	16.2 (2.2)	19.4 (3.0)	21.2 (22.0)
Organs extravascular mean transit time	min	6.27 (1.8)	5.12 (1.1)	-9.48 (29.0)
RE for R1b at 20min	%	17.0 (2.2)	24.1 (4.9)	41.3 (17.0)
RE for Sb at 20min	%	16.0 (5.3)	21.2 (6.3)	68.8 (100.0)

Table 1.5: Mean values along with their 95 percent confidence intervals for all systemic biomarkers at the control and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

1.4. Comparison to reference values

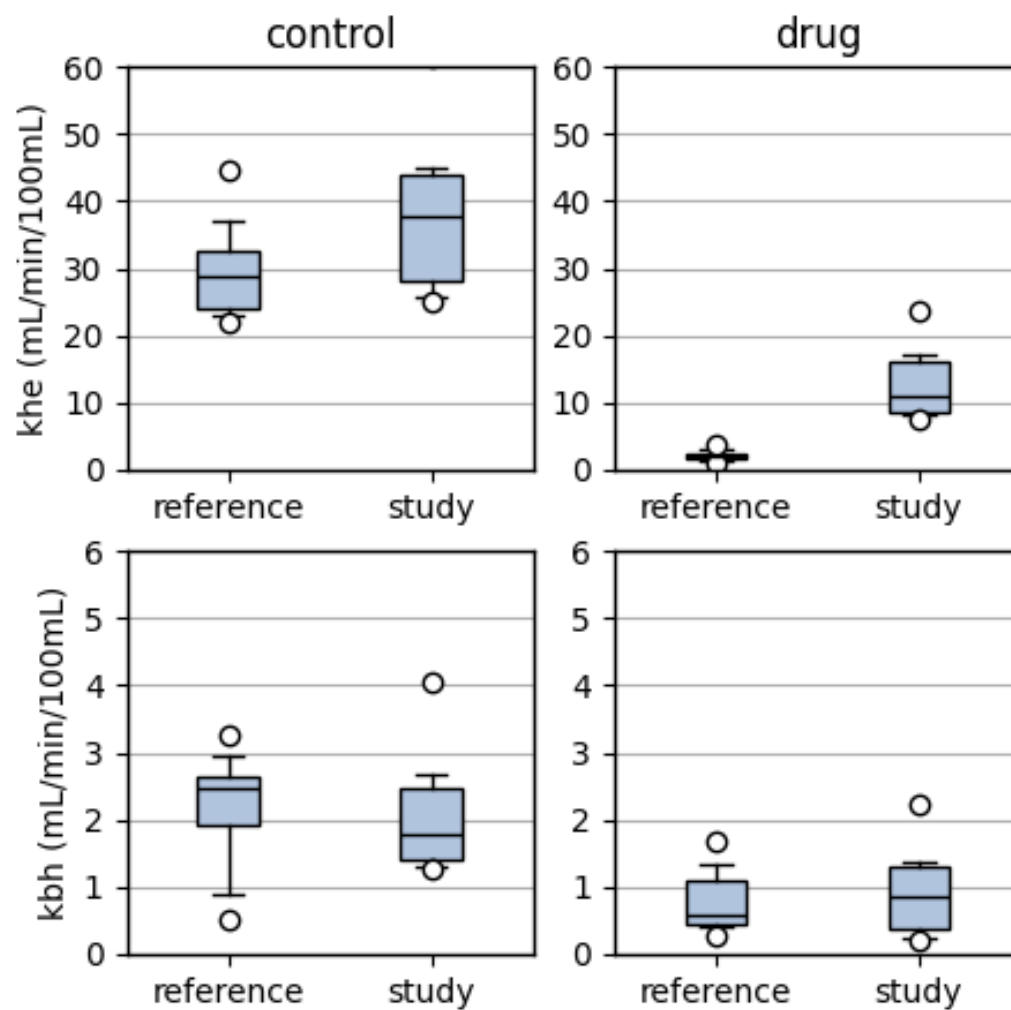


Figure 1.2: Comparison to reference values in healthy volunteers treated with the drug and under control conditions.

1.4.1. Control

Biomarker	Units	p-value	Bayes Factor	Power
Extracellular mean transit time	sec	0.05197	1.81	0.36
Liver T1-MOLLI at baseline	sec	0.07573	1.5	0.51
Final hepatocellular uptake rate	mL/min/100cm3	0.11396	1.09	0.35
Hepatocellular uptake rate	mL/min/100cm3	0.17531	0.91	0.38
Extracellular dispersion	%	0.35258	0.59	0.12
Hepatocellular tissue uptake rate	mL/min/100cm3	0.3885	0.57	0.1
Initial hepatocellular uptake rate	mL/min/100cm3	0.48218	0.52	0.12
Initial biliary excretion rate	mL/min/100cm3	0.51765	0.51	0.1
Liver blood clearance	L/min	0.55971	0.5	0.12
Hepatocellular mean transit time	min	0.61991	0.48	0.07
Liver extracellular volume fraction	mL/100cm3	0.62378	0.48	0.07
RE for R1l at 20min	%	0.63664	0.47	0.07
Final biliary excretion rate	mL/min/100cm3	0.67158	0.46	0.06
Liver T1-MOLLI at 45min	sec	0.74368	0.45	0.06
AUC for CI (0-35min)	mM*sec	0.85893	0.44	0.05
Liver T1-MOLLI at scan 2	sec	0.93067	0.44	0.05
AUC for CI (0-inf)	mM*sec	0.96072	0.44	0.05
Biliary excretion rate	mL/min/100cm3	0.96579	0.44	0.05
Biliary tissue excretion rate	mL/min/100cm3	0.98706	0.44	0.05
RE for SI at 20min	%	0.98727	0.44	0.05
Hematocrit	%			

Table 1.6: Results of a pairwise comparison testing for differences in liver biomarkers between this study and healthy reference data, under control conditions.

Biomarker	Units	p-value	Bayes Factor	Power
Body extraction fraction	%	0.06706	1.51	0.33
Heart-lung mean transit time	sec	0.09349	1.22	0.28
Cardiac output	L/min	0.22356	0.74	0.2
Organs extraction fraction	%	0.29351	0.64	0.14
Heart-lung dispersion	%	0.31667	0.64	0.2
RE for R1b at 20min	%	0.4631	0.53	0.09
AUC for Cb (0-35min)	mM*sec	0.49087	0.52	0.08
AUC for Cb (0-inf)	mM*sec	0.6965	0.46	0.06
Organs blood mean transit time	sec	0.70927	0.46	0.06
Organs extravascular mean transit time	min	0.74534	0.45	0.06
RE for Sb at 20min	%	0.89459	0.44	0.05

Table 1.7: Results of a pairwise comparison testing for differences in aorta biomarkers between this study and healthy reference data, under control conditions.

1.4.2. Treatment

Biomarker	Units	p-value	Bayes Factor	Power
Hepatocellular tissue uptake rate	mL/min/100cm ³	3e-05	10500.0	1.0
RE for SI at 20min	%	0.00013	1722.82	1.0
RE for R1l at 20min	%	0.00111	229.01	1.0
AUC for CI (0-35min)	mM*sec	0.00161	204.15	1.0
Final hepatocellular uptake rate	mL/min/100cm ³	0.00416	64.74	1.0
Liver T1-MOLLI at scan 2	sec	0.0044	13.6	0.95
Hepatocellular uptake rate	mL/min/100cm ³	0.00738	27.22	1.0
AUC for CI (0-inf)	mM*sec	0.01151	14.82	0.98
Liver blood clearance	L/min	0.02021	7.59	0.95
Initial hepatocellular uptake rate	mL/min/100cm ³	0.0335	3.97	0.85
Liver T1-MOLLI at 45min	sec	0.05691	1.88	0.59
Liver T1-MOLLI at baseline	sec	0.05946	1.62	0.43
Extracellular mean transit time	sec	0.08233	1.32	0.4
Liver extracellular volume fraction	mL/100cm ³	0.27045	0.7	0.22
Final biliary excretion rate	mL/min/100cm ³	0.34318	0.62	0.15
Initial biliary excretion rate	mL/min/100cm ³	0.39227	0.58	0.11
Extracellular dispersion	%	0.48789	0.53	0.11
Biliary tissue excretion rate	mL/min/100cm ³	0.51911	0.52	0.11
Biliary excretion rate	mL/min/100cm ³	0.63232	0.49	0.08
Hepatocellular mean transit time	min	0.83075	0.46	0.06
Hematocrit	%			

Table 1.8: Results of a pairwise comparison testing for differences in liver biomarkers between this study and healthy reference data, under treatment conditions.

Biomarker	Units	p-value	Bayes Factor	Power
Organs extraction fraction	%	0.03558	2.22	0.56
Organs extravascular mean transit time	min	0.09122	1.24	0.37
Heart-lung mean transit time	sec	0.12742	1.09	0.39
AUC for Cb (0-35min)	mM*sec	0.46518	0.54	0.12
Body extraction fraction	%	0.50402	0.53	0.1
Organs blood mean transit time	sec	0.54587	0.51	0.08
AUC for Cb (0-inf)	mM*sec	0.59529	0.5	0.08
RE for R1b at 20min	%	0.75914	0.46	0.06
RE for Sb at 20min	%	0.8456	0.46	0.05
Cardiac output	L/min	0.92609	0.45	0.05
Heart-lung dispersion	%	0.96182	0.45	0.05

Table 1.9: Results of a pairwise comparison testing for differences in aorta biomarkers between this study and healthy reference data, under treatment conditions.

1.5. Case notes
1.5.1. Subject SHF-002

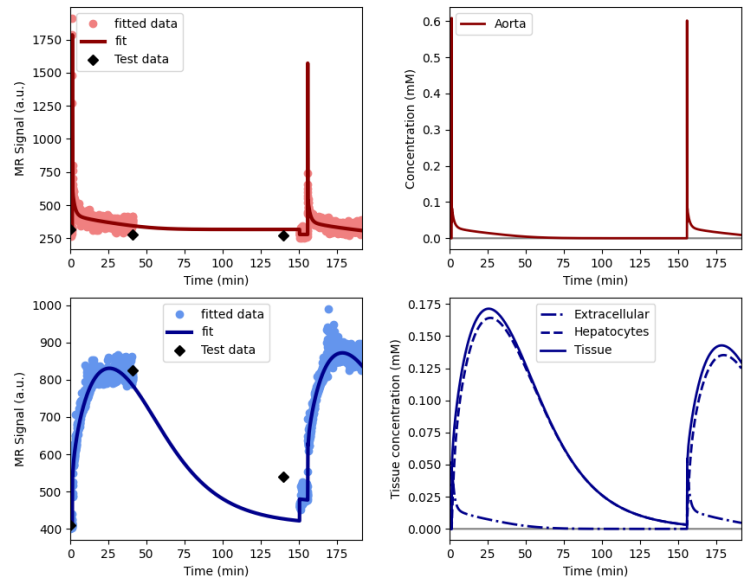


Figure 1.3: Signal-time curves for subject SHF-002 at the control visit.

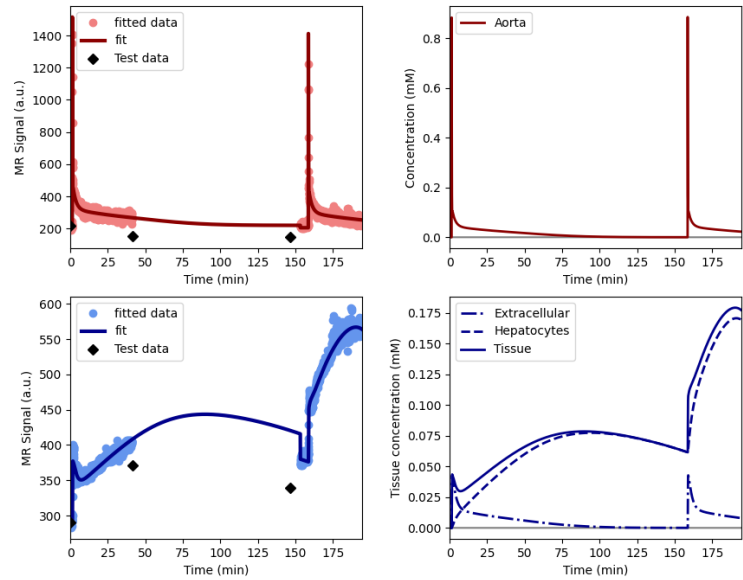


Figure 1.4: Signal-time curves for subject SHF-002 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	289.16	121.23	-58.07
AUC for Cl (0-inf)	mM*sec	727.59	782.3	7.52
Biliary excretion rate	mL/min/100cm3	2.67	0.25	-90.57
Biliary tissue excretion rate	mL/min/100cm3	3.71	0.31	-91.61
Extracellular dispersion	%	90.97	88.81	-2.38
Extracellular mean transit time	sec	21.34	48.36	126.6
Final biliary excretion rate	mL/min/100cm3	2.8	1.92	-31.56
Final hepatocellular uptake rate	mL/min/100cm3	35.96	13.77	-61.72
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	26.94	321.0	1091.66
Hepatocellular tissue uptake rate	mL/min/100cm3	142.17	42.99	-69.76
Hepatocellular uptake rate	mL/min/100cm3	40.04	8.27	-79.33
Initial biliary excretion rate	mL/min/100cm3	2.54	0.13	-94.71
Initial hepatocellular uptake rate	mL/min/100cm3	44.11	2.78	-93.69
Liver T1-MOLLI at 45min	sec	0.33	0.59	78.97
Liver T1-MOLLI at baseline	sec	0.73	0.78	6.09
Liver T1-MOLLI at scan 2	sec	0.62	0.59	-4.79
Liver blood clearance	L/min	0.06	0.06	-9.46
Liver extracellular volume fraction	mL/100cm3	28.16	19.25	-31.65
RE for R1l at 20min	%	120.92	31.81	-73.7
RE for Sl at 20min	%	93.65	30.06	-67.91

Table 1.10: Values for liver of subject SHF-002

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	43.88	79.31	80.74
AUC for Cb (0-inf)	mM*sec	59.05	139.35	135.99
Body extraction fraction	%	3.91	4.79	22.35
Cardiac output	L/min	8.77	3.03	-65.42
Heart-lung dispersion	%	26.36	36.86	39.84
Heart-lung mean transit time	sec	11.12	18.75	68.6
Organs blood mean transit time	sec	15.85	34.9	120.2
Organs extraction fraction	%	15.36	21.68	41.13
Organs extravascular mean transit time	min	3.79	4.88	28.95
RE for R1b at 20min	%	20.21	34.39	70.16
RE for Sb at 20min	%	7.45	30.23	305.91

Table 1.11: Values for aorta of subject SHF-002

1.5.2. Subject SHF-004

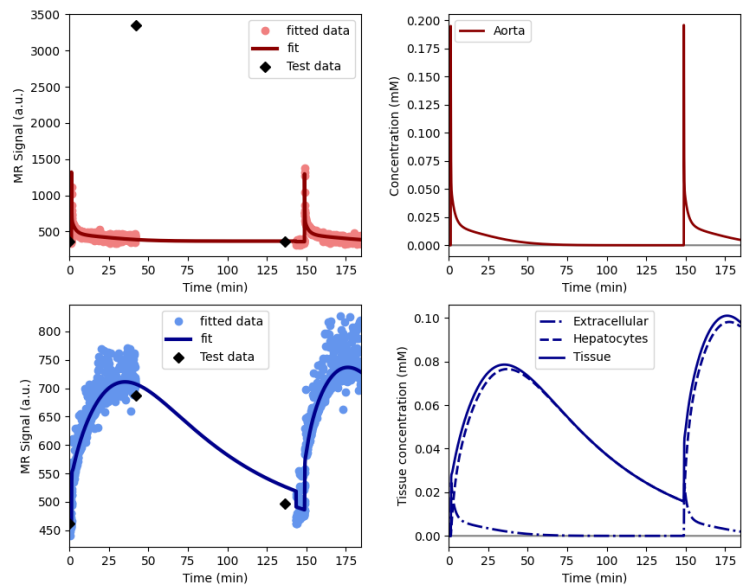


Figure 1.5: Signal-time curves for subject SHF-004 at the control visit.

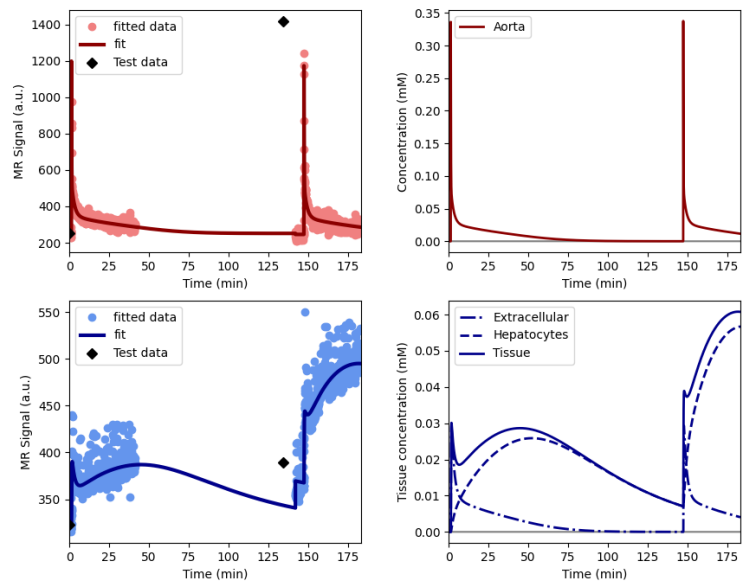


Figure 1.6: Signal-time curves for subject SHF-004 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	136.94	61.96	-54.75
AUC for Cl (0-inf)	mM*sec	483.67	209.5	-56.69
Biliary excretion rate	mL/min/100cm3	1.26	1.37	8.92
Biliary tissue excretion rate	mL/min/100cm3	1.62	1.7	4.67
Extracellular dispersion	%	91.54	84.66	-7.51
Extracellular mean transit time	sec	20.7	30.83	48.89
Final biliary excretion rate	mL/min/100cm3	1.62	1.84	13.13
Final hepatocellular uptake rate	mL/min/100cm3	29.37	11.47	-60.95
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	61.71	58.95	-4.46
Hepatocellular tissue uptake rate	mL/min/100cm3	113.04	39.06	-65.44
Hepatocellular uptake rate	mL/min/100cm3	25.08	7.43	-70.36
Initial biliary excretion rate	mL/min/100cm3	1.03	1.1	6.41
Initial hepatocellular uptake rate	mL/min/100cm3	20.8	3.4	-83.66
Liver T1-MOLLI at 45min	sec	0.51	0.78	51.75
Liver T1-MOLLI at baseline	sec	0.8	0.78	-2.19
Liver T1-MOLLI at scan 2	sec	0.69	0.69	0.19
Liver blood clearance	L/min	0.22	0.06	-72.07
Liver extracellular volume fraction	mL/100cm3	22.19	19.03	-14.24
RE for R1l at 20min	%	55.93	18.65	-66.65
RE for Sl at 20min	%	49.08	15.63	-68.16

Table 1.12: Values for liver of subject SHF-004

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	28.56	46.16	61.61
AUC for Cb (0-inf)	mM*sec	36.04	70.86	96.61
Body extraction fraction	%	5.29	4.85	-8.35
Cardiac output	L/min	10.66	5.92	-44.52
Heart-lung dispersion	%	76.16	57.17	-24.94
Heart-lung mean transit time	sec	12.62	17.04	34.98
Organs blood mean transit time	sec	23.85	25.35	6.28
Organs extraction fraction	%	12.53	20.49	63.5
Organs extravascular mean transit time	min	5.0	4.31	-13.88
RE for R1b at 20min	%	16.31	25.61	57.01
RE for Sb at 20min	%	21.43	27.57	28.67

Table 1.13: Values for aorta of subject SHF-004

1.5.3. Subject SHF-005

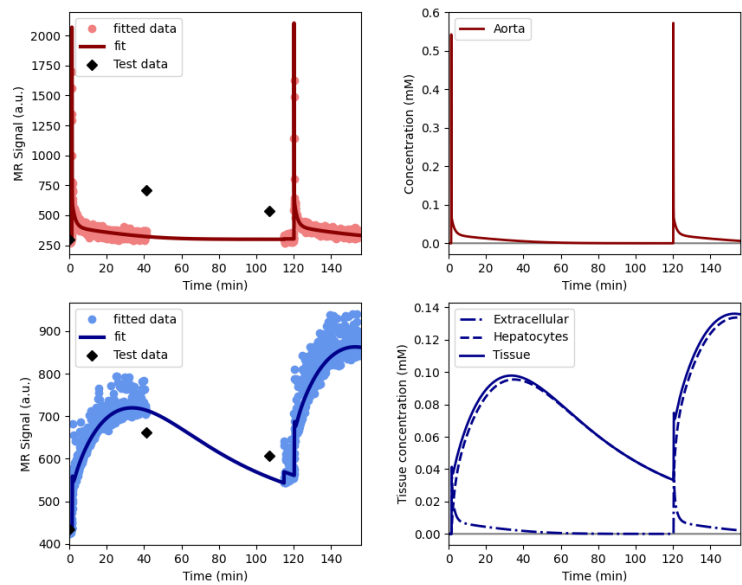


Figure 1.7: Signal-time curves for subject SHF-005 at the control visit.

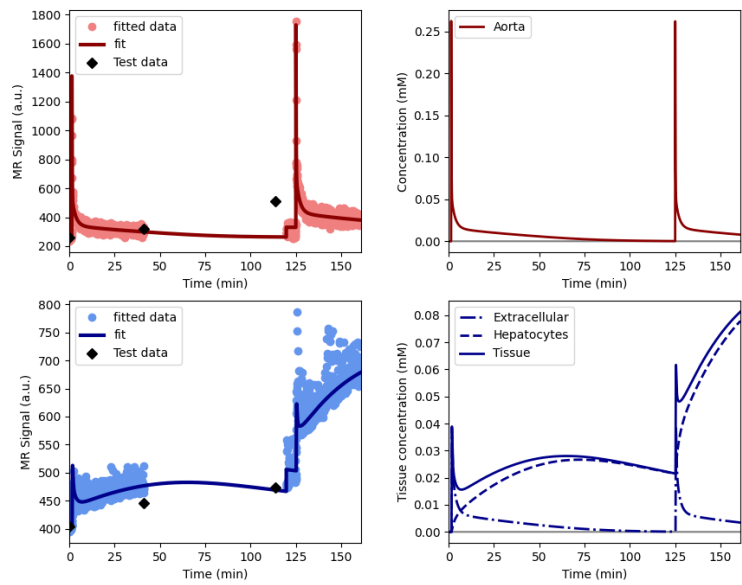


Figure 1.8: Signal-time curves for subject SHF-005 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	173.43	55.42	-68.04
AUC for Cl (0-inf)	mM*sec	601.74	260.13	-56.77
Biliary excretion rate	mL/min/100cm3	1.3	0.69	-47.01
Biliary tissue excretion rate	mL/min/100cm3	1.61	0.91	-43.55
Extracellular dispersion	%	64.27	57.85	-9.99
Extracellular mean transit time	sec	24.51	27.2	10.98
Final biliary excretion rate	mL/min/100cm3	1.09	0.49	-55.24
Final hepatocellular uptake rate	mL/min/100cm3	26.97	15.09	-44.04
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	62.24	110.25	77.14
Hepatocellular tissue uptake rate	mL/min/100cm3	137.09	41.09	-70.03
Hepatocellular uptake rate	mL/min/100cm3	25.82	9.79	-62.09
Initial biliary excretion rate	mL/min/100cm3	1.63	1.19	-26.9
Initial hepatocellular uptake rate	mL/min/100cm3	24.67	4.48	-81.83
Liver T1-MOLLI at 45min	sec	0.49	0.71	43.83
Liver T1-MOLLI at baseline	sec	0.79	0.79	0.33
Liver T1-MOLLI at scan 2	sec	0.57	0.72	26.2
Liver blood clearance	L/min	0.23	0.09	-61.8
Liver extracellular volume fraction	mL/100cm3	18.83	23.82	26.47
RE for R1l at 20min	%	69.98	15.67	-77.61
RE for Sl at 20min	%	65.71	20.39	-68.97

Table 1.14: Values for liver of subject SHF-005

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	33.84	29.78	-11.98
AUC for Cb (0-inf)	mM*sec	43.72	50.27	14.98
Body extraction fraction	%	5.8	5.56	-4.15
Cardiac output	L/min	5.34	4.82	-9.75
Heart-lung dispersion	%	42.17	56.36	33.64
Heart-lung mean transit time	sec	9.37	18.66	99.19
Organs blood mean transit time	sec	24.58	32.19	30.94
Organs extraction fraction	%	18.65	23.53	26.13
Organs extravascular mean transit time	min	4.09	5.42	32.4
RE for R1b at 20min	%	19.72	22.25	12.81
RE for Sb at 20min	%	19.43	12.57	-35.34

Table 1.15: Values for aorta of subject SHF-005

1.5.4. Subject SHF-006

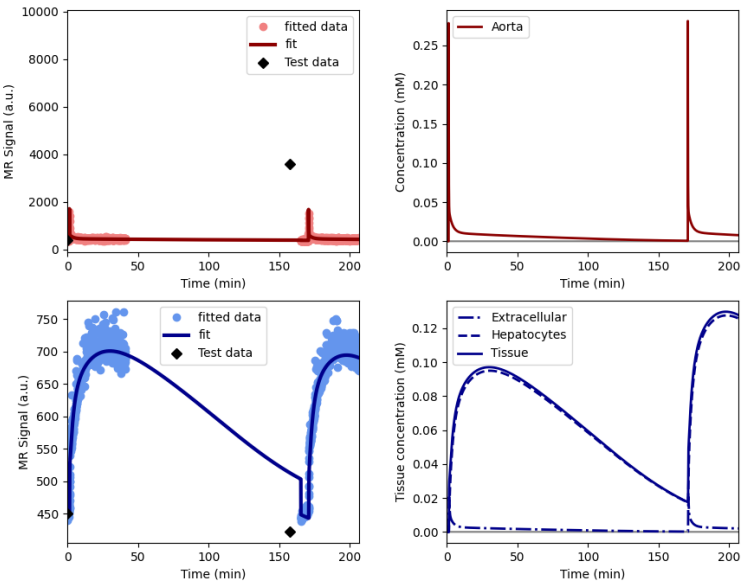


Figure 1.9: Signal-time curves for subject SHF-006 at the control visit.

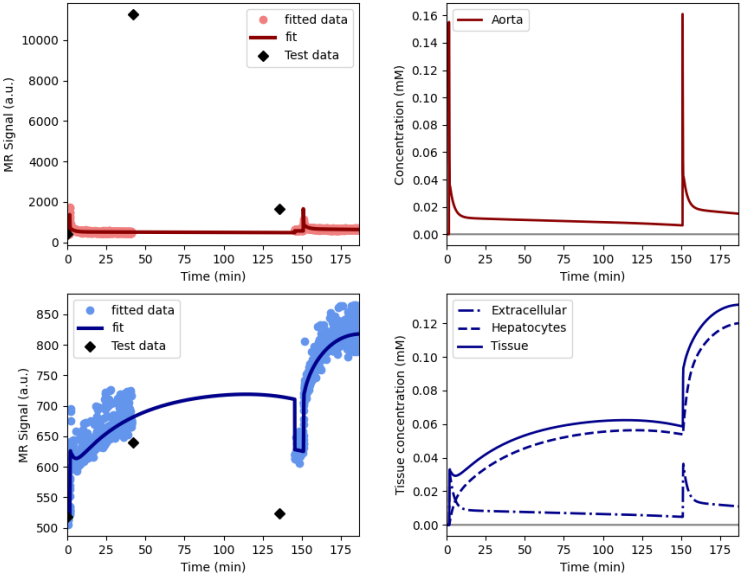


Figure 1.10: Signal-time curves for subject SHF-006 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	190.16	96.44	-49.29
AUC for Cl (0-inf)	mM*sec	693.53	597.3	-13.87
Biliary excretion rate	mL/min/100cm3	4.06	2.22	-45.22
Biliary tissue excretion rate	mL/min/100cm3	4.72	3.71	-21.41
Extracellular dispersion	%	61.8	75.79	22.63
Extracellular mean transit time	sec	24.88	35.44	42.43
Final biliary excretion rate	mL/min/100cm3	3.87	2.52	-35.01
Final hepatocellular uptake rate	mL/min/100cm3	67.99	34.32	-49.52
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	21.18	26.95	27.24
Hepatocellular tissue uptake rate	mL/min/100cm3	435.65	58.81	-86.5
Hepatocellular uptake rate	mL/min/100cm3	61.49	23.61	-61.61
Initial biliary excretion rate	mL/min/100cm3	4.25	1.99	-53.29
Initial hepatocellular uptake rate	mL/min/100cm3	54.98	12.89	-76.55
Liver T1-MOLLI at 45min	sec	0.68	0.57	-16.44
Liver T1-MOLLI at baseline	sec	0.68	0.72	5.99
Liver T1-MOLLI at scan 2	sec	0.64	0.62	-3.46
Liver blood clearance	L/min	0.67	0.25	-62.91
Liver extracellular volume fraction	mL/100cm3	14.11	40.14	184.42
RE for R1l at 20min	%	63.54	28.0	-55.93
RE for Sl at 20min	%	55.72	23.27	-58.23

Table 1.16: Values for liver of subject SHF-006

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	24.7	29.07	17.72
AUC for Cb (0-inf)	mM*sec	57.13	103.69	81.51
Body extraction fraction	%	3.32	1.02	-69.46
Cardiac output	L/min	9.77	9.54	-2.39
Heart-lung dispersion	%	70.76	46.54	-34.23
Heart-lung mean transit time	sec	9.84	29.96	204.34
Organs blood mean transit time	sec	37.77	25.23	-33.19
Organs extraction fraction	%	20.02	21.04	5.08
Organs extravascular mean transit time	min	8.11	7.72	-4.91
RE for R1b at 20min	%	14.75	18.92	28.27
RE for Sb at 20min	%	8.85	15.37	73.73

Table 1.17: Values for aorta of subject SHF-006

1.5.5. Subject SHF-009

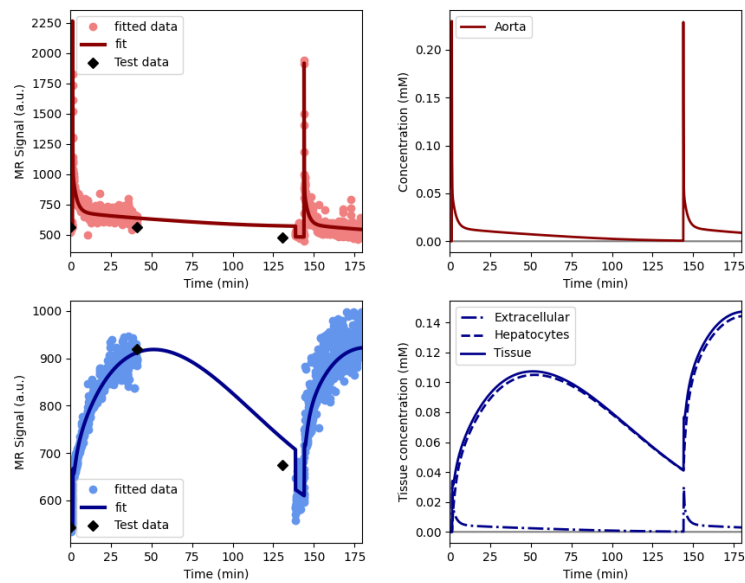


Figure 1.11: Signal-time curves for subject SHF-009 at the control visit.

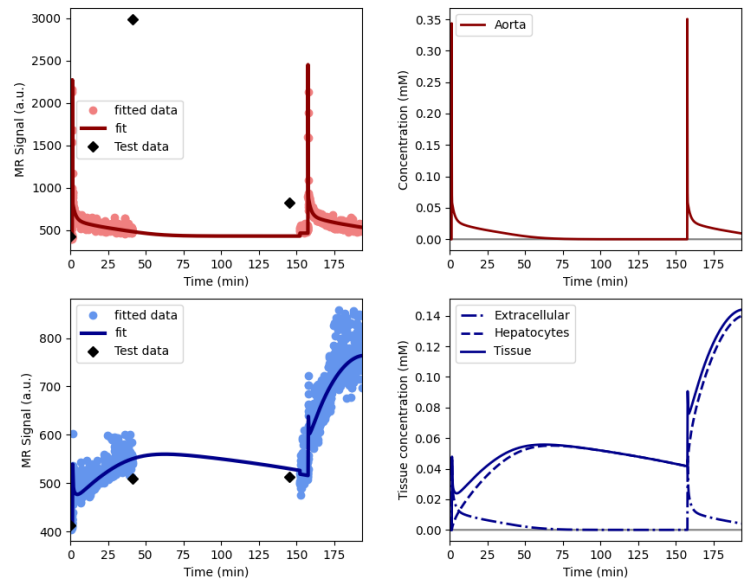


Figure 1.12: Signal-time curves for subject SHF-009 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	171.67	100.54	-41.44
AUC for Cl (0-inf)	mM*sec	827.28	554.62	-32.96
Biliary excretion rate	mL/min/100cm ³	1.83	0.22	-88.05
Biliary tissue excretion rate	mL/min/100cm ³	2.24	0.29	-87.15
Extracellular dispersion	%	59.37	64.96	9.42
Extracellular mean transit time	sec	18.88	18.94	0.29
Final biliary excretion rate	mL/min/100cm ³	1.95	0.8	-59.1
Final hepatocellular uptake rate	mL/min/100cm ³	40.82	19.37	-52.56
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	44.66	347.61	678.31
Hepatocellular tissue uptake rate	mL/min/100cm ³	191.8	51.85	-72.97
Hepatocellular uptake rate	mL/min/100cm ³	35.23	12.48	-64.57
Initial biliary excretion rate	mL/min/100cm ³	1.72	0.13	-92.64
Initial hepatocellular uptake rate	mL/min/100cm ³	29.64	5.6	-81.12
Liver T1-MOLLI at 45min	sec	0.42	0.58	38.61
Liver T1-MOLLI at baseline	sec	0.76	0.74	-3.05
Liver T1-MOLLI at scan 2	sec	0.52	0.57	10.03
Liver blood clearance	L/min	0.28	0.1	-63.03
Liver extracellular volume fraction	mL/100cm ³	18.37	24.07	31.04
RE for R1l at 20min	%	65.19	28.21	-56.73
RE for Sl at 20min	%	60.06	22.76	-62.1

Table 1.18: Values for liver of subject SHF-009

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	29.47	41.6	41.16
AUC for Cb (0-inf)	mM*sec	60.58	57.5	-5.08
Body extraction fraction	%	3.2	4.11	28.37
Cardiac output	L/min	13.46	11.43	-15.06
Heart-lung dispersion	%	83.04	43.62	-47.47
Heart-lung mean transit time	sec	9.71	13.59	39.96
Organs blood mean transit time	sec	28.03	24.91	-11.13
Organs extraction fraction	%	16.28	14.61	-10.26
Organs extravascular mean transit time	min	7.61	3.58	-52.95
RE for R1b at 20min	%	17.79	26.36	48.19
RE for Sb at 20min	%	15.1	26.85	77.76

Table 1.19: Values for aorta of subject SHF-009

1.5.6. Subject SHF-017

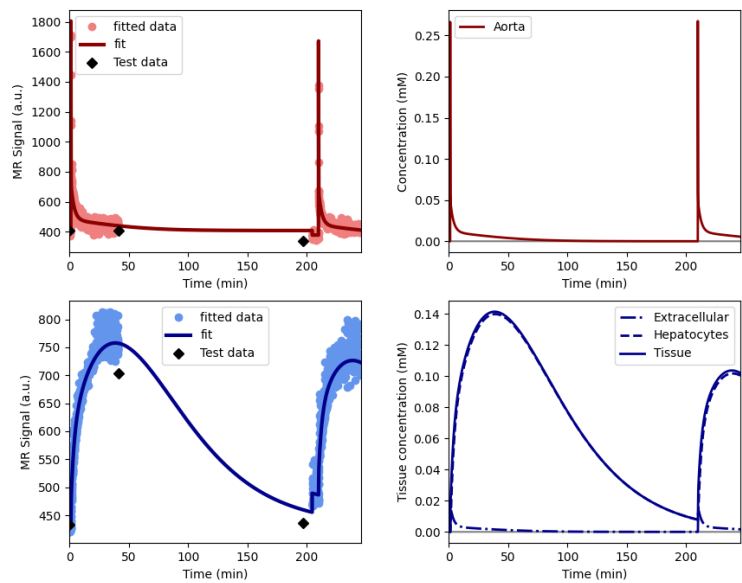


Figure 1.13: Signal-time curves for subject SHF-017 at the control visit.

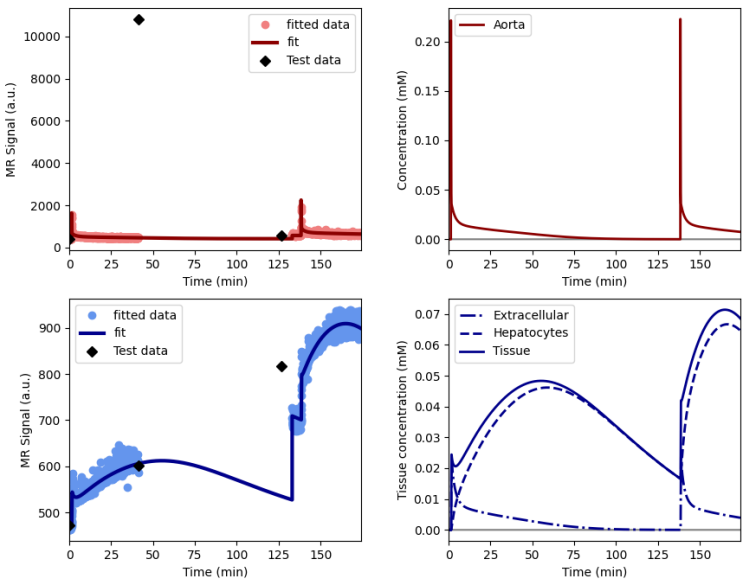


Figure 1.14: Signal-time curves for subject SHF-017 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for CI (0-35min)	mM*sec	214.73	80.2	-62.65
AUC for CI (0-inf)	mM*sec	903.91	357.85	-60.41
Biliary excretion rate	mL/min/100cm3	1.76	1.05	-40.23
Biliary tissue excretion rate	mL/min/100cm3	2.1	1.48	-29.54
Extracellular dispersion	%	88.8	73.96	-16.7
Extracellular mean transit time	sec	33.08	33.12	0.12
Final biliary excretion rate	mL/min/100cm3	2.18	2.65	21.6
Final hepatocellular uptake rate	mL/min/100cm3	39.48	25.16	-36.27
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	47.68	67.67	41.92
Hepatocellular tissue uptake rate	mL/min/100cm3	282.81	60.14	-78.73
Hepatocellular uptake rate	mL/min/100cm3	45.08	17.26	-61.72
Initial biliary excretion rate	mL/min/100cm3	1.48	0.66	-55.57
Initial hepatocellular uptake rate	mL/min/100cm3	50.68	9.35	-81.55
Liver T1-MOLLI at 45min	sec	0.37	0.54	44.92
Liver T1-MOLLI at baseline	sec	0.65	0.7	8.9
Liver T1-MOLLI at scan 2	sec	0.69	0.53	-23.26
Liver blood clearance	L/min	0.45	0.19	-58.16
Liver extracellular volume fraction	mL/100cm3	15.94	28.7	80.01
RE for R1l at 20min	%	80.54	24.04	-70.15
RE for Sl at 20min	%	70.42	21.94	-68.84

Table 1.20: Values for liver of subject SHF-017

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	24.2	27.07	11.89
AUC for Cb (0-inf)	mM*sec	39.11	44.59	13.99
Body extraction fraction	%	5.11	3.65	-28.56
Cardiac output	L/min	10.11	12.43	22.95
Heart-lung dispersion	%	48.46	42.39	-12.52
Heart-lung mean transit time	sec	14.13	15.88	12.38
Organs blood mean transit time	sec	26.63	27.59	3.62
Organs extraction fraction	%	14.6	14.83	1.62
Organs extravascular mean transit time	min	9.0	4.82	-46.49
RE for R1b at 20min	%	13.16	17.29	31.33
RE for Sb at 20min	%	23.5	14.63	-37.74

Table 1.21: Values for aorta of subject SHF-017

2

One-scan results

2.1. Data summary

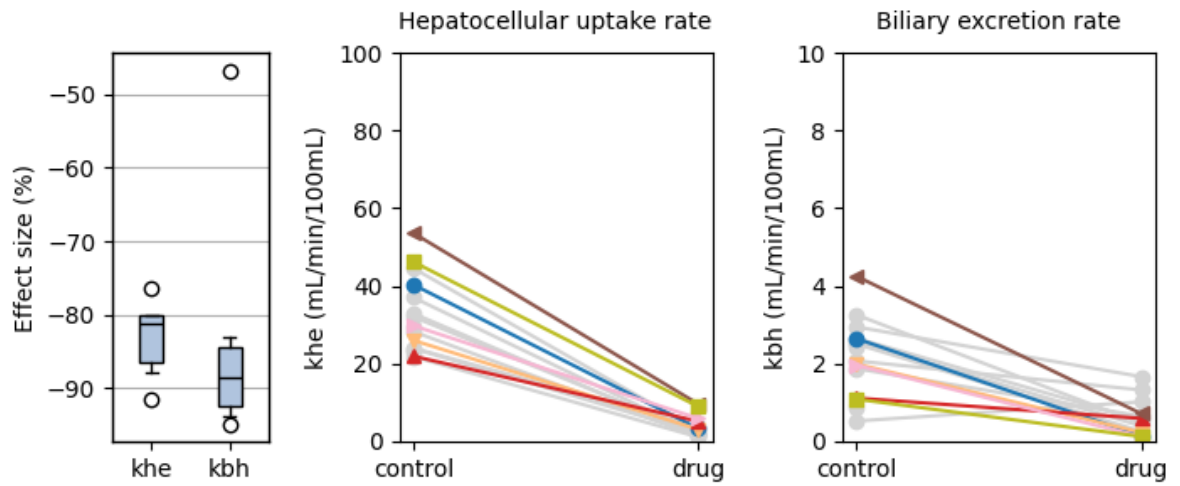


Figure 2.1: Effect size (%) on hepatocellular uptake (k_{he} , left) and biliary excretion (k_{bh} , right) of gadoxetate. The boxplot shows median, interquartile range and 95 percent range. The line plots show individual values for hepatocellular uptake (k_{he} , middle) and biliary excretion (k_{bh} , right) of gadoxetate of the control (left of plot) and treatment (right of plot). Grey lines are healthy controls with rifampicin injection.

	parameter	count	mean	std	min	25%	50%	75%	max
	khe effect size (%)	6.0	-83.0	5.6	-91.5	-86.4	-81.2	-80.1	-76.3
	khe control (mL/min/100cm3)	6.0	36.3	12.39	21.93	26.95	35.04	44.72	53.59
	khe drug (mL/min/100cm3)	6.0	6.07	2.77	3.14	3.86	5.58	8.26	9.69
	kbh effect size (%)	6.0	-82.6	18.0	-94.8	-92.4	-88.5	-84.5	-46.7
	kbh control (mL/min/100cm3)	6.0	2.17	1.17	1.09	1.33	1.98	2.48	4.24
	kbh drug (mL/min/100cm3)	6.0	0.32	0.26	0.12	0.13	0.18	0.5	0.72

Table 2.1: Effect size and absolute values of hepatocellular uptake (k_{he}) and biliary excretion (k_{bh}) of gadoxetate

2.2. Liver biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for CI (0-35min)	0.00216	22.14	152.88
AUC for CI (0-inf)	0.01456	5.2	14.03
Biliary excretion rate	0.00841	7.86	51.87
Biliary tissue excretion rate	0.00609	10.04	59.98
Extracellular dispersion	0.615	0.42	1.72
Extracellular mean transit time	0.23171	0.72	0.29
Hematocrit			
Hepatocellular mean transit time	0.01614	4.82	0.02
Hepatocellular tissue uptake rate	0.00672	9.32	88.82
Hepatocellular uptake rate	0.00091	43.14	448.62
Liver T1-MOLLI at 45min	0.03842	2.53	0.07
Liver T1-MOLLI at baseline	0.27107	0.65	0.53
Liver blood clearance	0.01433	5.27	23.36
Liver extracellular volume fraction	0.06456	1.74	0.06
RE for R11 at 20min	0.00148	29.51	241.98
RE for SI at 20min	0.00101	39.6	343.49

Table 2.2: Results of a pairwise comparison testing for differences in liver biomarkers between control and treatment. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for CI (0-35min)	mM*sec	196.0 (51.0)	66.0 (14.0)	-65.0 (7.5)
AUC for CI (0-inf)	mM*sec	892.0 (200.0)	572.0 (140.0)	-34.8 (14.0)
Biliary excretion rate	mL/min/100cm3	2.17 (0.94)	0.321 (0.21)	-82.6 (14.0)
Biliary tissue excretion rate	mL/min/100cm3	2.61 (1.0)	0.435 (0.31)	-81.0 (16.0)
Extracellular dispersion	%	80.0 (11.0)	76.6 (7.3)	-2.26 (15.0)
Extracellular mean transit time	sec	34.6 (10.0)	41.7 (6.0)	28.4 (25.0)
Hematocrit	%	45.0 (0.0)	45.0 (0.0)	0.0 (0.0)
Hepatocellular mean transit time	min	46.6 (17.0)	395.0 (190.0)	844.0 (500.0)
Hepatocellular tissue uptake rate	mL/min/100cm3	215.0 (87.0)	24.4 (6.1)	-87.3 (3.7)
Hepatocellular uptake rate	mL/min/100cm3	36.3 (9.9)	6.07 (2.2)	-83.0 (4.5)
Liver T1-MOLLI at 45min	sec	0.469 (0.1)	0.629 (0.075)	40.3 (25.0)
Liver T1-MOLLI at baseline	sec	0.734 (0.048)	0.751 (0.028)	2.68 (4.0)
Liver blood clearance	L/min	0.295 (0.15)	0.0578 (0.028)	-78.0 (6.9)
Liver extracellular volume fraction	mL/100cm3	17.9 (2.4)	24.0 (3.8)	39.7 (40.0)
RE for R11 at 20min	%	75.7 (18.0)	24.5 (5.1)	-66.5 (7.0)
RE for SI at 20min	%	65.3 (15.0)	21.4 (4.5)	-66.5 (6.7)

Table 2.3: Mean values along with their 95 percent confidence intervals for all liver biomarkers of the control and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

2.3. Systemic biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for Cb (0-35min)	0.1004	1.27	0.25
AUC for Cb (0-inf)	0.08274	1.45	0.14
Body extraction fraction	0.13072	1.05	5.99
Cardiac output	0.3524	0.56	1.63
Heart-lung dispersion	0.92231	0.38	0.89
Heart-lung mean transit time	0.77644	0.39	1.21
Organs blood mean transit time	0.75255	0.39	0.74
Organs extraction fraction	0.48391	0.47	0.58
Organs extravascular mean transit time	0.24371	0.7	3.19
RE for R1b at 20min	0.01054	6.63	0.07
RE for Sb at 20min	0.20047	0.79	0.25

Table 2.4: Results of a pairwise comparison testing for differences in systemic biomarkers between control and treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	32.3 (6.5)	44.4 (16.0)	34.8 (28.0)
AUC for Cb (0-inf)	mM*sec	64.9 (9.0)	99.6 (35.0)	52.3 (42.0)
Body extraction fraction	%	4.46 (1.5)	2.98 (0.73)	-24.2 (30.0)
Cardiac output	L/min	7.65 (2.5)	6.88 (2.0)	-4.87 (25.0)
Heart-lung dispersion	%	56.0 (17.0)	57.1 (10.0)	15.4 (36.0)
Heart-lung mean transit time	sec	17.2 (3.1)	16.8 (3.3)	-1.38 (13.0)
Organs blood mean transit time	sec	34.4 (7.0)	36.1 (9.3)	11.7 (39.0)
Organs extraction fraction	%	19.0 (3.1)	20.5 (5.0)	8.08 (21.0)
Organs extravascular mean transit time	min	8.61 (2.1)	6.82 (2.4)	-18.8 (29.0)
RE for R1b at 20min	%	17.6 (2.3)	25.5 (5.6)	44.4 (18.0)
RE for Sb at 20min	%	17.4 (6.2)	22.7 (4.7)	64.0 (76.0)

Table 2.5: Mean values along with their 95 percent confidence intervals for all systemic biomarkers at the control and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

2.4. Case notes
2.4.1. Subject SHF-002

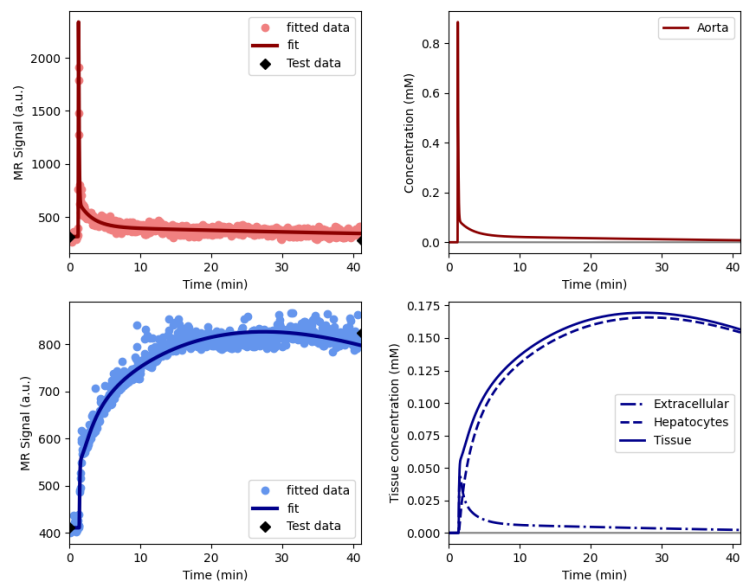


Figure 2.2: Signal-time curves for subject SHF-002 at the control visit.

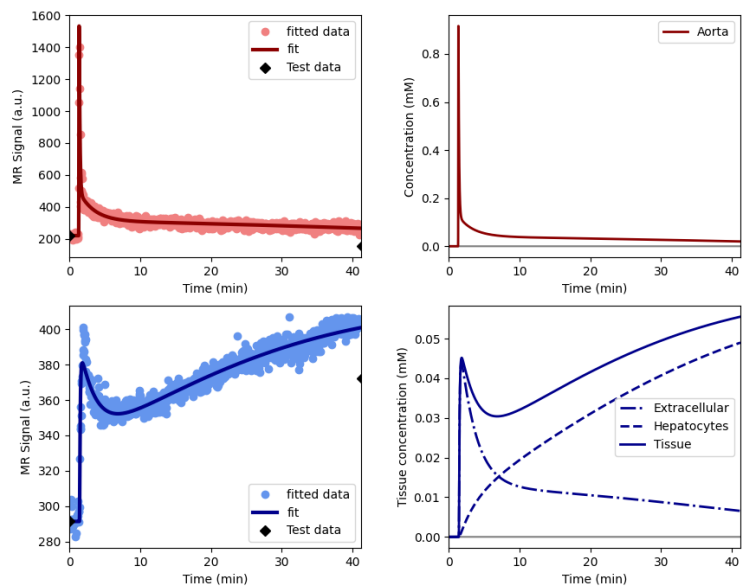


Figure 2.3: Signal-time curves for subject SHF-002 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	306.78	85.29	-72.2
AUC for Cl (0-inf)	mM*sec	948.11	779.34	-17.8
Biliary excretion rate	mL/min/100cm3	2.64	0.14	-94.81
Biliary tissue excretion rate	mL/min/100cm3	3.13	0.17	-94.67
Extracellular dispersion	%	74.51	87.81	17.85
Extracellular mean transit time	sec	31.09	47.16	51.69
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	32.0	600.0	1775.11
Hepatocellular tissue uptake rate	mL/min/100cm3	261.54	19.31	-92.62
Hepatocellular uptake rate	mL/min/100cm3	40.31	3.41	-91.53
Liver T1-MOLLI at 45min	sec	0.33	0.59	78.97
Liver T1-MOLLI at baseline	sec	0.73	0.78	6.09
Liver blood clearance	L/min	0.07	0.02	-62.89
Liver extracellular volume fraction	mL/100cm3	15.41	17.69	14.76
RE for R1l at 20min	%	119.37	32.51	-72.76
RE for Sl at 20min	%	100.48	27.41	-72.72

Table 2.6: Values for liver of subject SHF-002

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	46.7	83.03	77.82
AUC for Cb (0-inf)	mM*sec	73.19	182.54	149.39
Body extraction fraction	%	6.97	3.63	-47.87
Cardiac output	L/min	3.97	2.93	-26.21
Heart-lung dispersion	%	40.72	56.73	39.32
Heart-lung mean transit time	sec	12.24	12.39	1.27
Organs blood mean transit time	sec	38.32	40.07	4.58
Organs extraction fraction	%	24.56	23.13	-5.82
Organs extravascular mean transit time	min	5.94	5.57	-6.36
RE for R1b at 20min	%	19.96	36.18	81.27
RE for Sb at 20min	%	7.13	21.76	205.31

Table 2.7: Values for aorta of subject SHF-002

2.4.2. Subject SHF-004

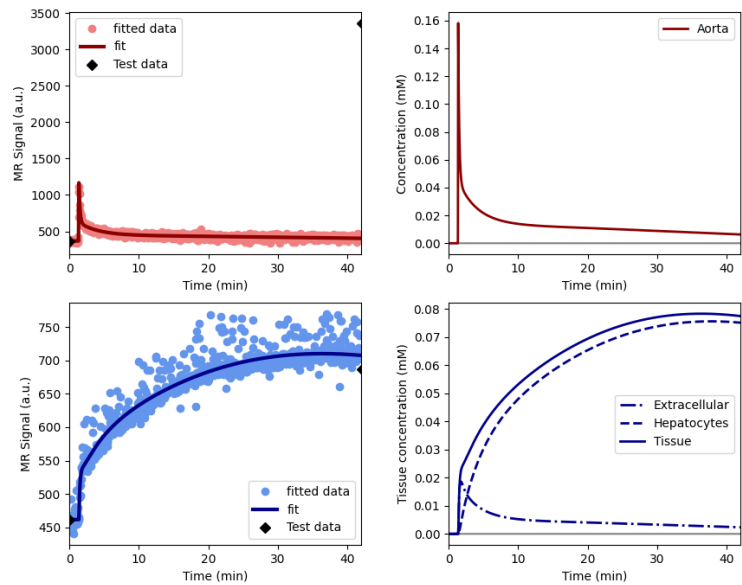


Figure 2.4: Signal-time curves for subject SHF-004 at the control visit.

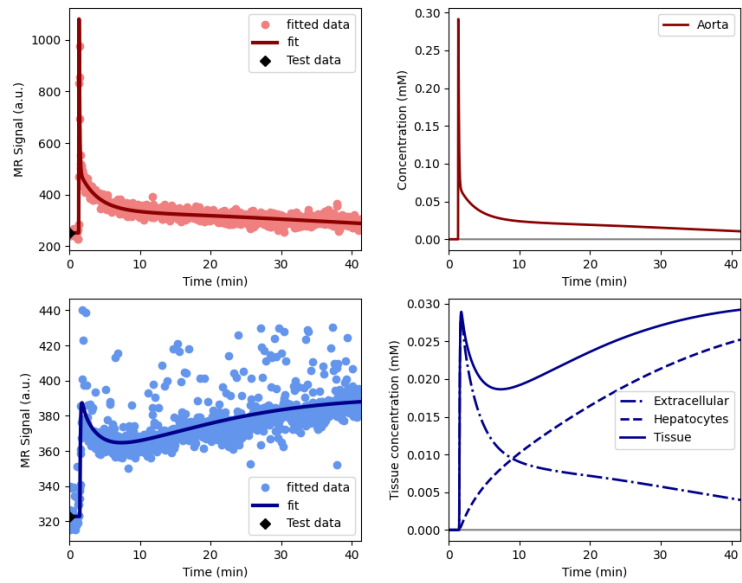


Figure 2.5: Signal-time curves for subject SHF-004 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for CI (0-35min)	mM*sec	130.8	48.63	-62.82
AUC for CI (0-inf)	mM*sec	603.27	359.77	-40.36
Biliary excretion rate	mL/min/100cm ³	1.99	0.23	-88.46
Biliary tissue excretion rate	mL/min/100cm ³	2.5	0.29	-88.43
Extracellular dispersion	%	91.68	70.41	-23.2
Extracellular mean transit time	sec	24.83	29.29	17.95
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	40.05	346.18	764.3
Hepatocellular tissue uptake rate	mL/min/100cm ³	128.59	15.35	-88.06
Hepatocellular uptake rate	mL/min/100cm ³	26.01	3.14	-87.94
Liver T1-MOLLI at 45min	sec	0.51	0.78	51.75
Liver T1-MOLLI at baseline	sec	0.8	0.78	-2.19
Liver blood clearance	L/min	0.23	0.03	-88.63
Liver extracellular volume fraction	mL/100cm ³	20.23	20.43	1.02
RE for R1l at 20min	%	55.44	18.46	-66.71
RE for Sl at 20min	%	49.08	15.67	-68.07

Table 2.8: Values for liver of subject SHF-004

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	28.87	47.99	66.25
AUC for Cb (0-inf)	mM*sec	59.99	92.11	53.54
Body extraction fraction	%	3.13	2.68	-14.16
Cardiac output	L/min	10.46	8.13	-22.29
Heart-lung dispersion	%	84.14	56.53	-32.82
Heart-lung mean transit time	sec	14.71	14.21	-3.38
Organs blood mean transit time	sec	30.6	23.21	-24.16
Organs extraction fraction	%	15.06	12.99	-13.71
Organs extravascular mean transit time	min	7.45	5.85	-21.45
RE for R1b at 20min	%	17.8	27.5	54.5
RE for Sb at 20min	%	21.43	27.58	28.71

Table 2.9: Values for aorta of subject SHF-004

2.4.3. Subject SHF-005

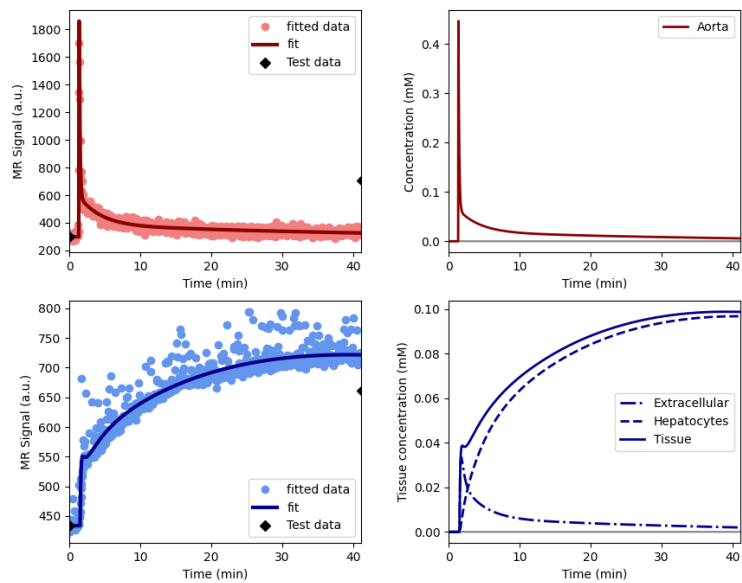


Figure 2.6: Signal-time curves for subject SHF-005 at the control visit.

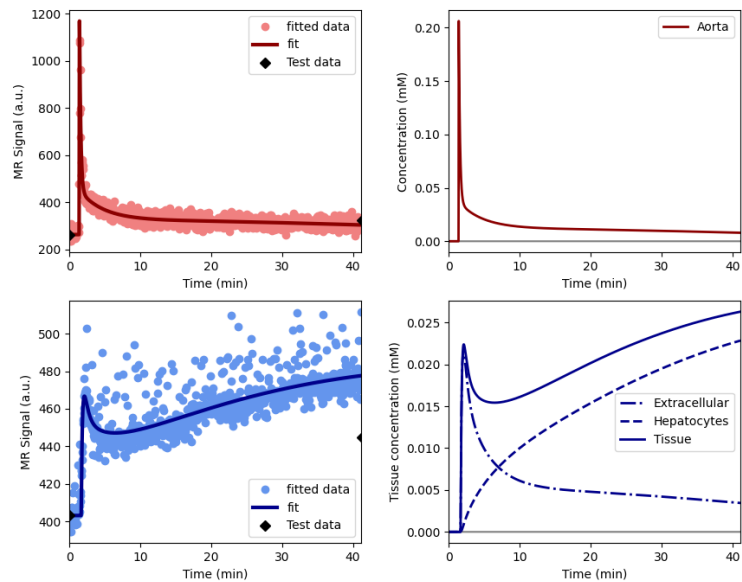


Figure 2.7: Signal-time curves for subject SHF-005 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	166.93	41.28	-75.27
AUC for Cl (0-inf)	mM*sec	807.61	343.46	-57.47
Biliary excretion rate	mL/min/100cm3	1.11	0.59	-46.74
Biliary tissue excretion rate	mL/min/100cm3	1.36	0.78	-43.07
Extracellular dispersion	%	71.57	67.4	-5.82
Extracellular mean transit time	sec	34.8	49.9	43.37
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	73.33	128.81	75.66
Hepatocellular tissue uptake rate	mL/min/100cm3	120.15	22.09	-81.62
Hepatocellular uptake rate	mL/min/100cm3	21.93	5.2	-76.31
Liver T1-MOLLI at 45min	sec	0.49	0.71	43.83
Liver T1-MOLLI at baseline	sec	0.79	0.79	0.33
Liver blood clearance	L/min	0.2	0.05	-76.13
Liver extracellular volume fraction	mL/100cm3	18.26	23.53	28.86
RE for R1l at 20min	%	69.43	16.03	-76.91
RE for Sl at 20min	%	57.64	13.43	-76.71

Table 2.10: Values for liver of subject SHF-005

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	35.93	29.24	-18.62
AUC for Cb (0-inf)	mM*sec	57.68	82.66	43.31
Body extraction fraction	%	6.64	2.4	-63.86
Cardiac output	L/min	3.53	5.29	49.68
Heart-lung dispersion	%	56.88	79.78	40.26
Heart-lung mean transit time	sec	14.58	15.7	7.68
Organs blood mean transit time	sec	44.22	52.9	19.62
Organs extraction fraction	%	16.51	19.32	17.03
Organs extravascular mean transit time	min	9.55	8.7	-8.88
RE for R1b at 20min	%	19.01	22.44	18.0
RE for Sb at 20min	%	22.93	21.25	-7.33

Table 2.11: Values for aorta of subject SHF-005

2.4.4. Subject SHF-006

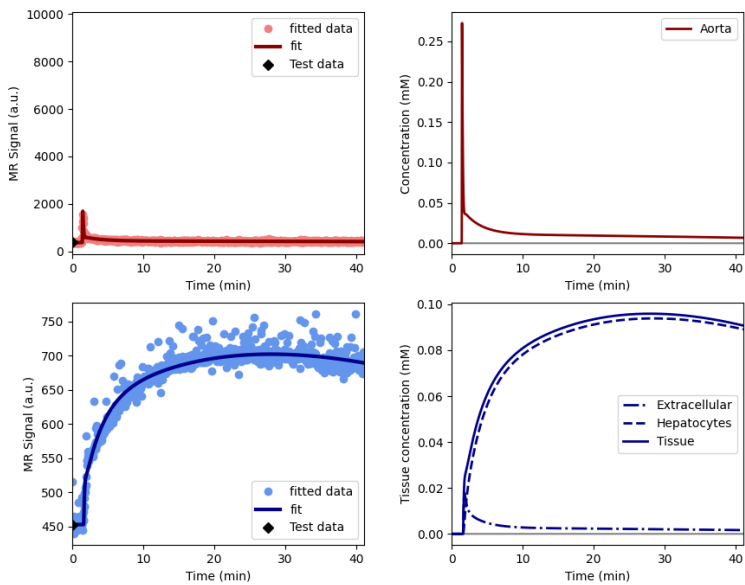


Figure 2.8: Signal-time curves for subject SHF-006 at the control visit.

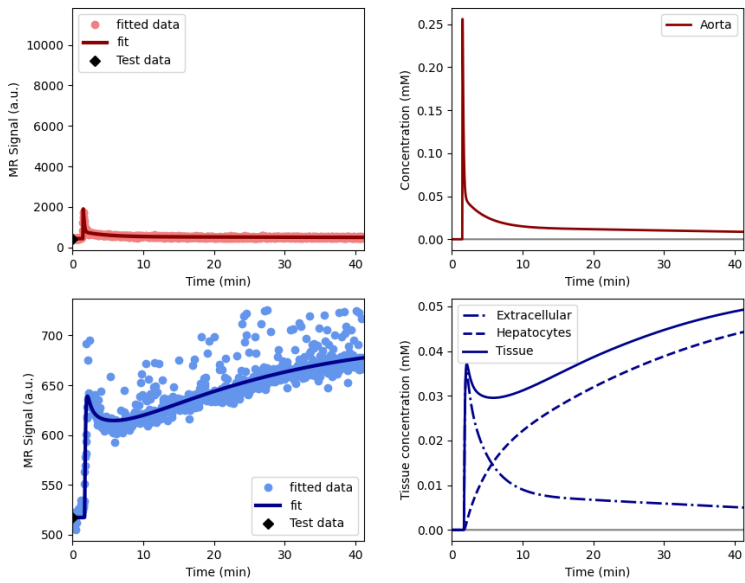


Figure 2.9: Signal-time curves for subject SHF-006 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	174.93	78.25	-55.27
AUC for Cl (0-inf)	mM*sec	747.2	659.98	-11.67
Biliary excretion rate	mL/min/100cm ³	4.24	0.72	-83.12
Biliary tissue excretion rate	mL/min/100cm ³	4.89	1.05	-78.61
Extracellular dispersion	%	62.75	69.82	11.27
Extracellular mean transit time	sec	28.12	44.38	57.85
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	20.46	95.63	367.45
Hepatocellular tissue uptake rate	mL/min/100cm ³	407.35	30.79	-92.44
Hepatocellular uptake rate	mL/min/100cm ³	53.59	9.69	-81.92
Liver T1-MOLLI at 45min	sec	0.68	0.57	-16.44
Liver T1-MOLLI at baseline	sec	0.68	0.72	5.99
Liver blood clearance	L/min	0.58	0.1	-82.53
Liver extracellular volume fraction	mL/100cm ³	13.16	31.48	139.26
RE for R1l at 20min	%	62.9	28.05	-55.41
RE for Sl at 20min	%	55.06	24.9	-54.78

Table 2.12: Values for liver of subject SHF-006

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	25.61	32.7	27.67
AUC for Cb (0-inf)	mM*sec	70.1	103.77	48.03
Body extraction fraction	%	2.61	1.71	-34.42
Cardiac output	L/min	8.92	6.51	-27.06
Heart-lung dispersion	%	39.32	50.91	29.49
Heart-lung mean transit time	sec	19.96	23.7	18.72
Organs blood mean transit time	sec	34.32	40.33	17.51
Organs extraction fraction	%	22.25	20.96	-5.82
Organs extravascular mean transit time	min	8.26	11.33	37.19
RE for R1b at 20min	%	15.69	19.26	22.78
RE for Sb at 20min	%	7.81	19.64	151.48

Table 2.13: Values for aorta of subject SHF-006

2.4.5. Subject SHF-009

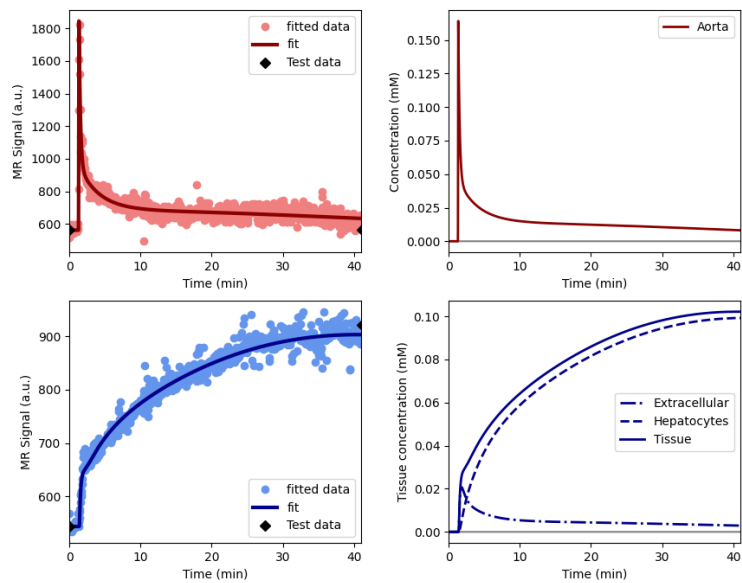


Figure 2.10: Signal-time curves for subject SHF-009 at the control visit.

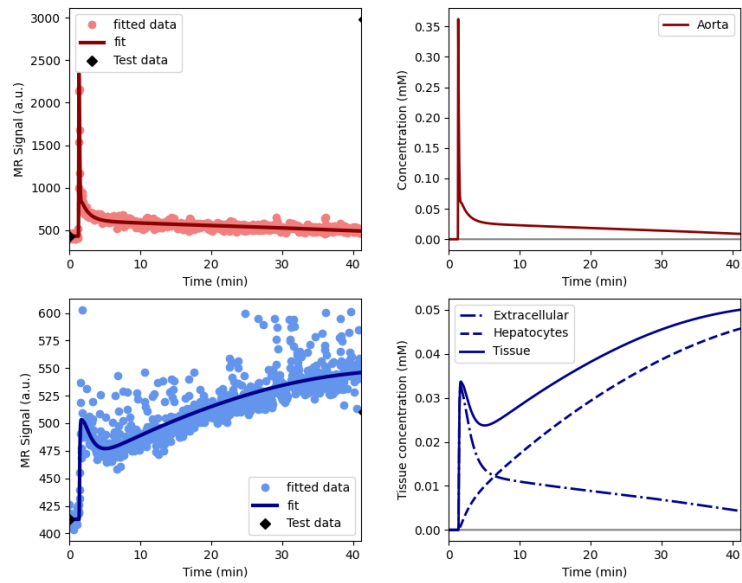


Figure 2.11: Signal-time curves for subject SHF-009 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	161.79	75.74	-53.19
AUC for Cl (0-inf)	mM*sec	898.36	612.54	-31.82
Biliary excretion rate	mL/min/100cm ³	1.96	0.12	-93.7
Biliary tissue excretion rate	mL/min/100cm ³	2.43	0.17	-93.14
Extracellular dispersion	%	79.71	87.7	10.02
Extracellular mean transit time	sec	28.64	36.8	28.5
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	41.17	600.0	1357.25
Hepatocellular tissue uptake rate	mL/min/100cm ³	154.15	22.96	-85.11
Hepatocellular uptake rate	mL/min/100cm ³	29.76	5.96	-79.97
Liver T1-MOLLI at 45min	sec	0.42	0.58	38.61
Liver T1-MOLLI at baseline	sec	0.76	0.74	-3.05
Liver blood clearance	L/min	0.24	0.05	-79.1
Liver extracellular volume fraction	mL/100cm ³	19.31	25.97	34.49
RE for R1l at 20min	%	65.59	28.29	-56.87
RE for Sl at 20min	%	60.52	25.15	-58.45

Table 2.14: Values for liver of subject SHF-009

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	31.95	44.74	40.01
AUC for Cb (0-inf)	mM*sec	79.36	74.83	-5.71
Body extraction fraction	%	2.97	4.27	43.98
Cardiac output	L/min	10.24	8.45	-17.48
Heart-lung dispersion	%	79.83	41.09	-48.53
Heart-lung mean transit time	sec	20.26	19.78	-2.35
Organs blood mean transit time	sec	39.66	22.23	-43.96
Organs extraction fraction	%	19.86	30.99	56.04
Organs extravascular mean transit time	min	7.2	2.44	-66.05
RE for R1b at 20min	%	20.18	29.8	47.72
RE for Sb at 20min	%	21.88	31.17	42.46

Table 2.15: Values for aorta of subject SHF-009

2.4.6. Subject SHF-017

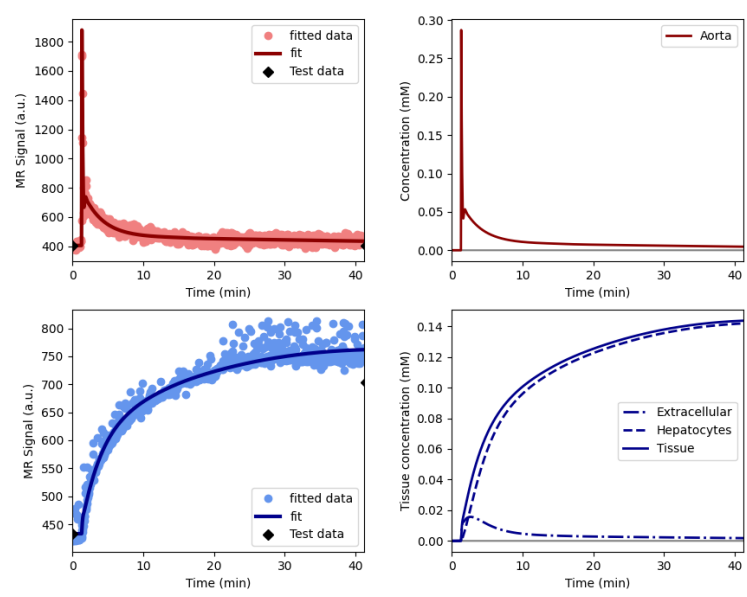


Figure 2.12: Signal-time curves for subject SHF-017 at the control visit.

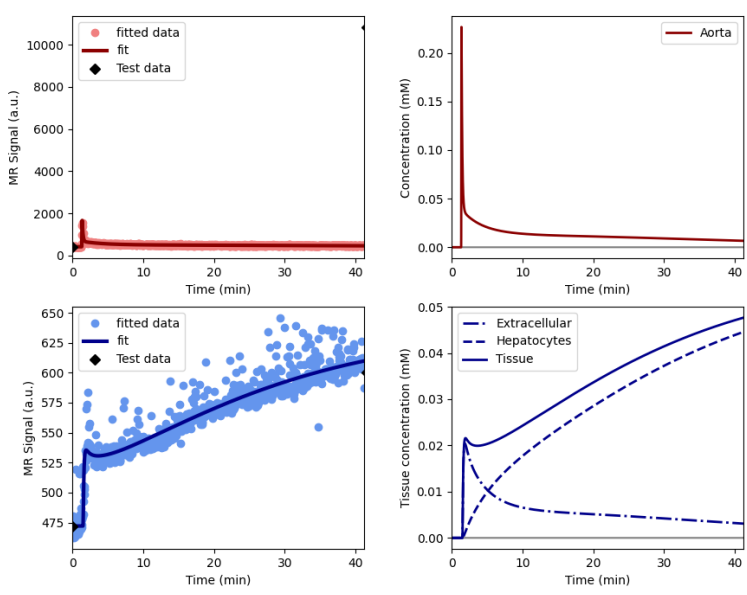


Figure 2.13: Signal-time curves for subject SHF-017 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for CI (0-35min)	mM*sec	233.09	66.73	-71.37
AUC for CI (0-inf)	mM*sec	1349.36	676.1	-49.9
Biliary excretion rate	mL/min/100cm3	1.09	0.12	-88.51
Biliary tissue excretion rate	mL/min/100cm3	1.37	0.17	-87.87
Extracellular dispersion	%	99.97	76.3	-23.68
Extracellular mean transit time	sec	59.96	42.77	-28.67
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	72.77	600.0	724.47
Hepatocellular tissue uptake rate	mL/min/100cm3	221.1	36.03	-83.7
Hepatocellular uptake rate	mL/min/100cm3	46.19	9.03	-80.45
Liver T1-MOLLI at 45min	sec	0.37	0.54	44.92
Liver T1-MOLLI at baseline	sec	0.65	0.7	8.9
Liver blood clearance	L/min	0.46	0.1	-78.63
Liver extracellular volume fraction	mL/100cm3	20.89	25.07	19.99
RE for R1l at 20min	%	81.2	23.94	-70.52
RE for Sl at 20min	%	69.26	21.94	-68.32

Table 2.16: Values for liver of subject SHF-017

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	24.76	28.64	15.69
AUC for Cb (0-inf)	mM*sec	49.03	61.55	25.53
Body extraction fraction	%	4.47	3.17	-28.99
Cardiac output	L/min	8.75	9.99	14.16
Heart-lung dispersion	%	35.13	57.79	64.52
Heart-lung mean transit time	sec	21.6	15.08	-30.19
Organs blood mean transit time	sec	19.38	38.12	96.75
Organs extraction fraction	%	15.66	15.78	0.76
Organs extravascular mean transit time	min	13.25	7.0	-47.16
RE for R1b at 20min	%	12.66	18.01	42.24
RE for Sb at 20min	%	23.14	14.63	-36.78

Table 2.17: Values for aorta of subject SHF-017

3

Secondary results

3.1. Diurnal variation

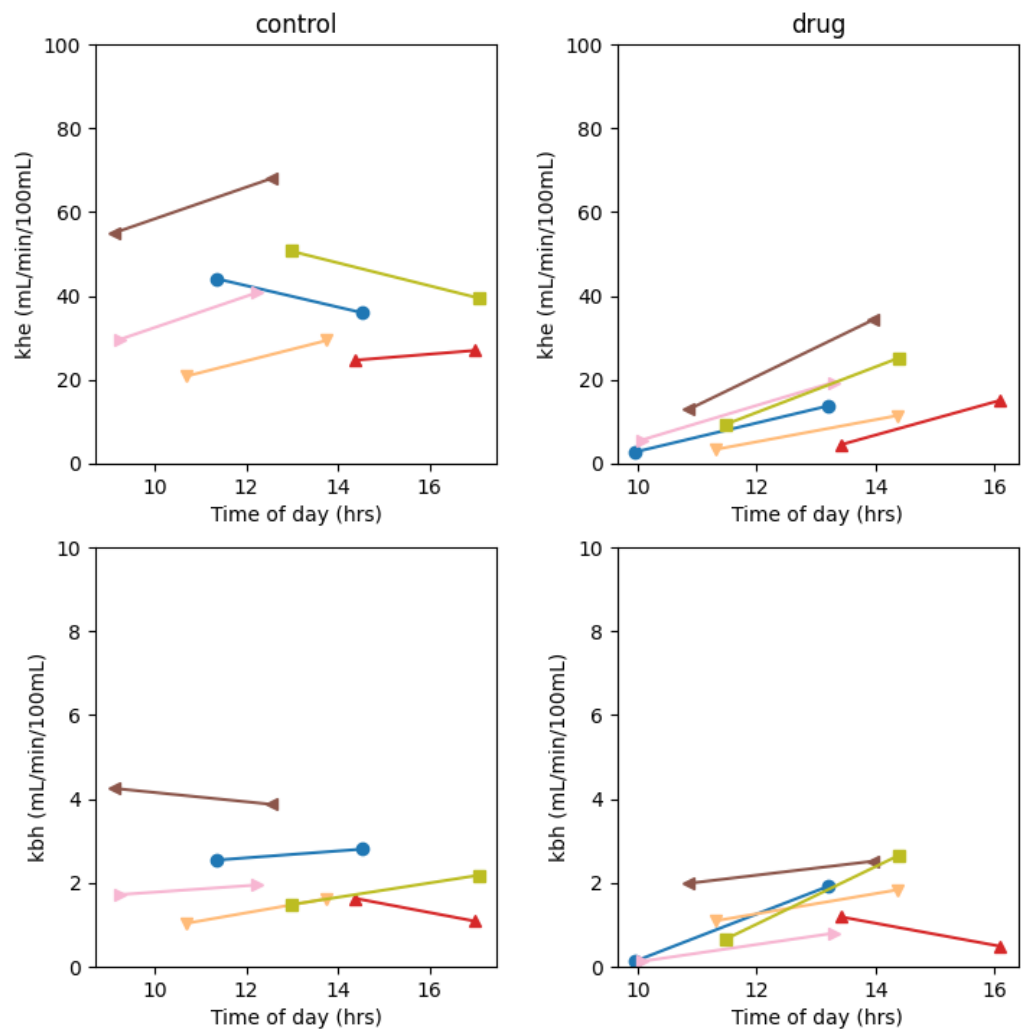


Figure 3.1: Intra-day changes in hepatocellular uptake (k_{he} , top row) and biliary excretion (k_{bh} , bottom row) of gadoxetate at for the control (left column) and treatment (right column). Full lines connect values taken in the same subject at the same day.