Online Data Supplement

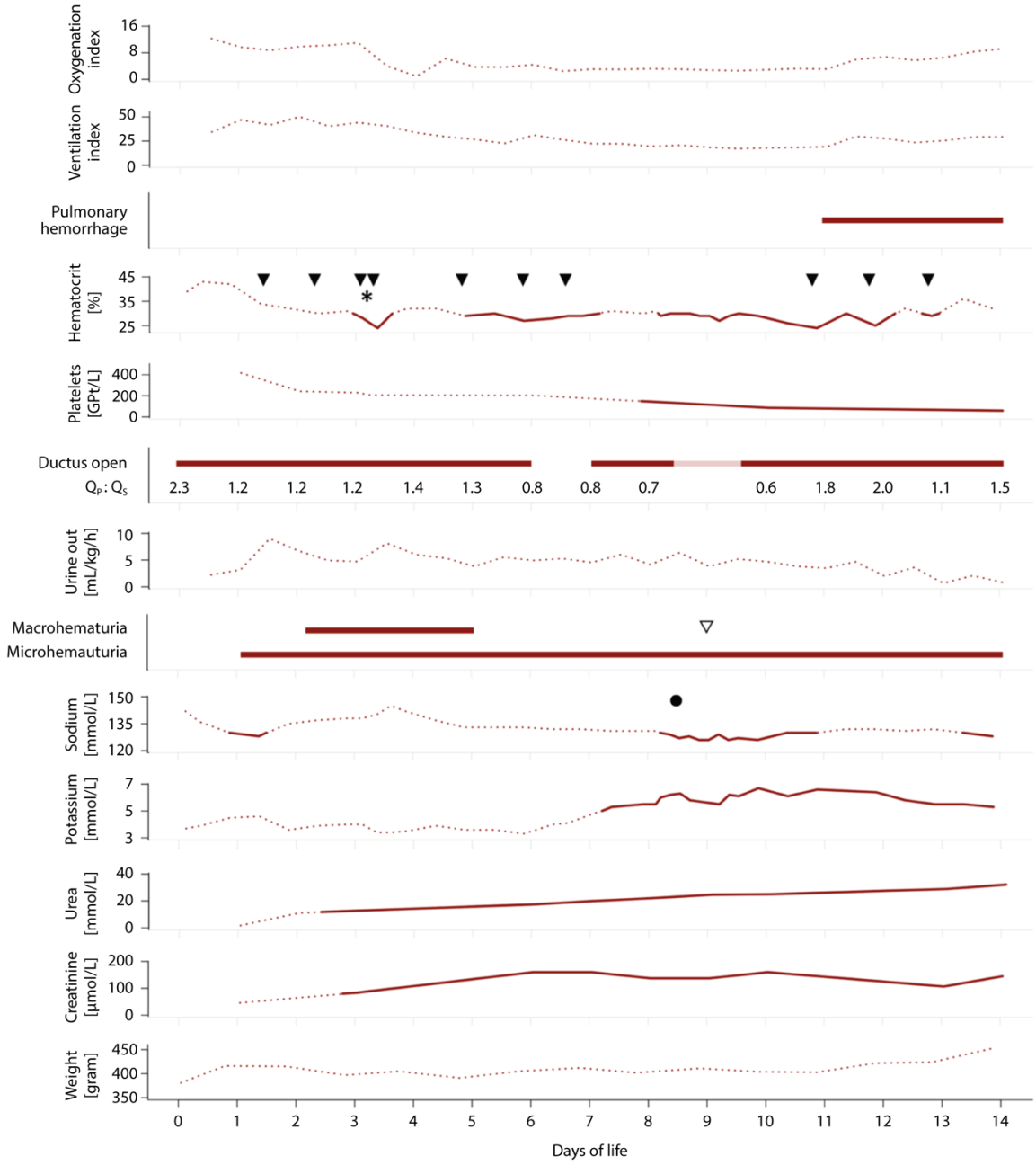
Supplementary Table

	Placebo (n = 5)	UC-MSC (n = 7)
Total lung surface		
Mean [cm^2 per cm^3 lung]	134.9	135.1
$CI_{95\%}$ of mean [cm^2 per cm^3 lung]	110.9 – 158.8	110.7 – 159.4
CV_{total}	0.143	0.195
thereof due to $CE_{stereol.}$ [%]	3.2	2.3
thereof due to $CV_{biol.}$ [%]	96.8	97.7
Surface in functional parenchyma		
Mean [cm^2 per cm^3 lung]	108.1	96.7
$CI_{95\%}$ of mean [cm^2 per cm^3 lung]	75.8 – 140.5	70.5 – 122.9
CV_{total}	0.241	0.293
thereof due to $CE_{stereol.}$ [%]	1.5	1.3
thereof due to $CV_{biol.}$ [%]	98.5	98.7
Volume fraction of functional parenchyma		
Mean [cm^3 per cm^3 lung]	0.559	0.501
$CI_{95\%}$ of mean [cm^3 per cm^3 lung]	0.451 – 0.667	0.397 – 0.617
CV_{total}	0.156	0.235
thereof due to $CE_{stereol.}$ [%]	8.1	4.8
thereof due to $CV_{biol.}$ [%]	91.9	95.2
Volume fraction of non-functional parenchyma		
Mean [cm^3 per cm^3 lung]	0.196	0.247
$CI_{95\%}$ of mean [cm^3 per cm^3 lung]	0.083 – 0.301	0.138 – 0.356
CV_{total}	0.463	0.478
thereof due to $CE_{stereol.}$ [%]	4.3	3.6
thereof due to $CV_{biol.}$ [%]	95.7	96.4

Abbreviations: $CI_{95\%}$ – 95% confidence interval of the mean, CV_{total} – observed overall coefficient of parameter variation, $CE_{stereol.}$ – calculated method-inherent coefficient of error, $CV_{biol.}$ – coefficient of biological variation, i.e., contribution of actual sample variance to observed overall coefficient of variation.

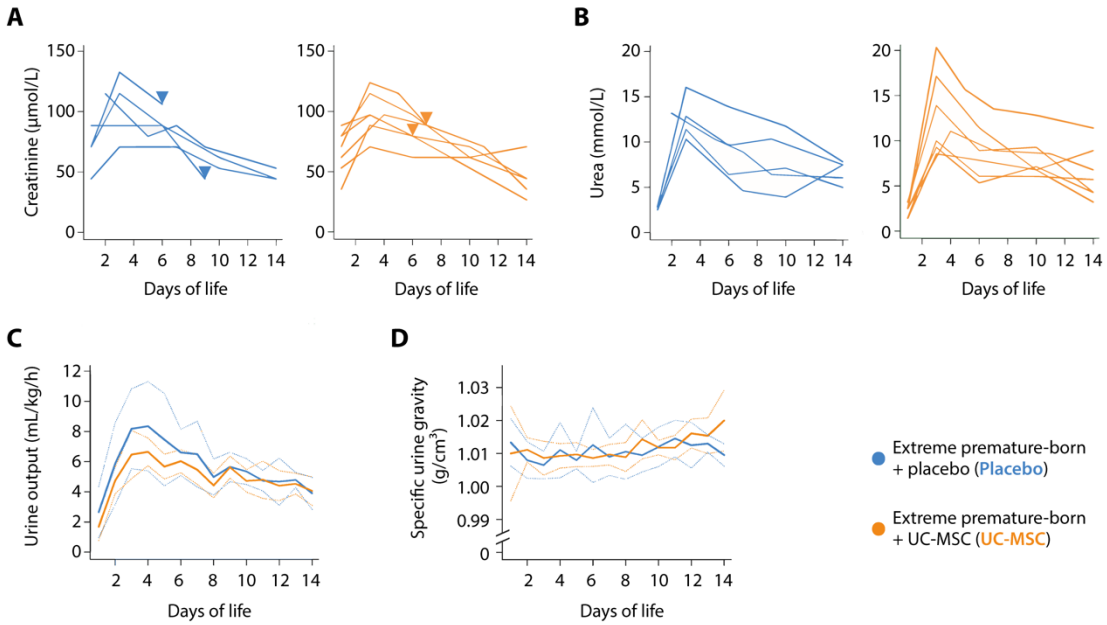
Supplementary Table S1. Derived stereological parameters.

Supplementary Figures

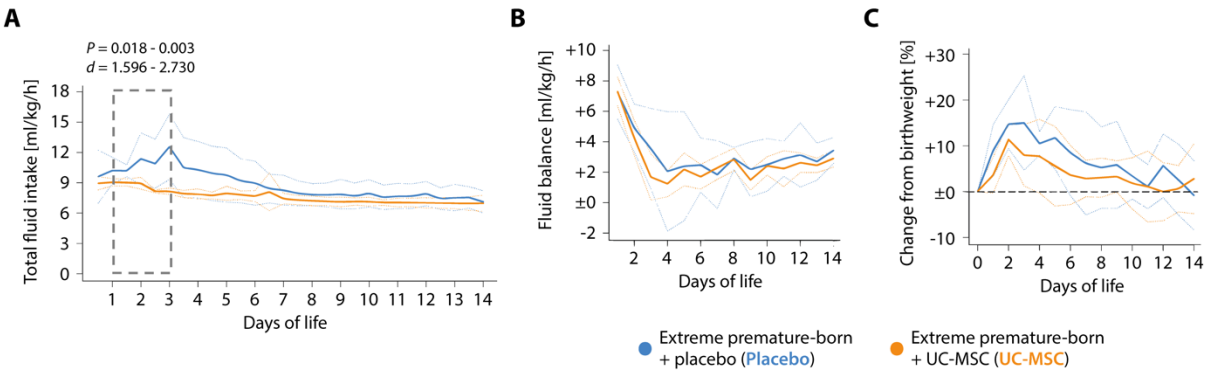


Supplementary Figure S1. Clinical course and temporal progression of adverse events in a single extremely premature-born baboon receiving intravenous UC-MSC over 2 minutes. Dotted lines indicate normal, solid lines pathological measurements. The latter were defined as follows: Hematocrit < 30%, platelets < 150 GPt/L, sodium < 130 mmol/L, potassium > 5.5 mmol/L, urea > 11.8 mmol/L (71 mg/dL, corresponding to 33 mg/dL blood urea nitrogen), creatinine > 80 µmol/L (0.9 mg/dL). GPt/L – 10^9 particles per liter. Closed triangles (▼) denote transfusions of packed blood cells, the asterisk (∗) a coagulation analysis revealing derailed intrinsic plasmatic coagulation with an activated partial prothrombin time (aPTT) of 55.5 sec (normal: < 35 sec), physiological prothrombin time/quick, and normal fibrinogen levels. Daily

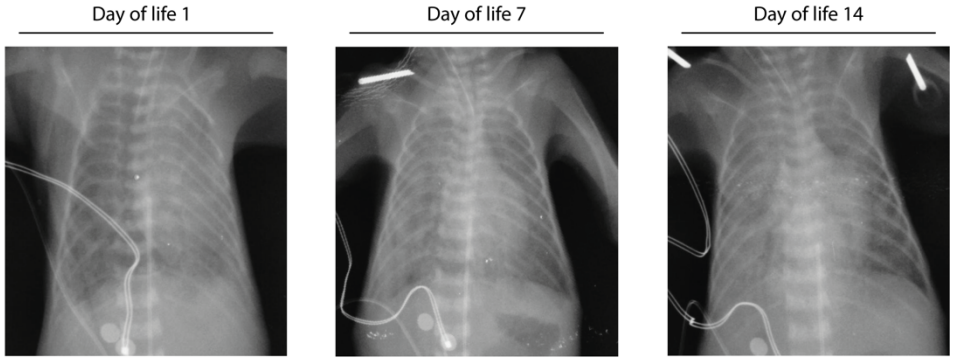
echocardiographic studies revealed no signs for acute pulmonary obstructions with age-physiological peak pulmonary valve velocities. Heart rates and blood pressures stayed within age-physiological ranges without the need for fluid boluses or vasoactive medication. We noted two episodes suspect of seizures on day of life 4. No paraclinical signs pointing to a systemic infection, in particular no thrombocytopenia, thrombocytosis, leukopenia, leukocytosis or fever were noted in this animal; blood cultures stayed negative. The open triangle (▽) indicates an ultrasonographic study of the kidneys, finding normal arterial and venous Doppler signals, physiologic kidney dimensions (left kidney 1.65 × 2.04 cm, estimated volume 2.62 cm^3; right kidney 1.59 × 2.46 cm, estimated volume 2.82 cm^3) and normal organ structures without signs for obstructions or infarctions. No echocardiography was performed on that day to spare the immature animal, as shown by the opaque overlay in the ductus diagram. The closed circle (●) denotes a combined serum/urine analysis, revealing a fractional sodium excretion of 21.64% with urine sodium levels exceeding 100 mmol/L. Throughout the 14-day clinical course, platelet counts as low as 60 GPt/L, blood urea nitrogen levels up to 32.1 mmol/L (90 mg/dL), corresponding to a total blood urea of 32.1 mmol/L (193 mg/dL); serum creatinine levels up to 160 µmol/l (2.1 mg/dL); hyperkalemia up to 6.7 mmol/L, hyponatremia as low as 126 mmol/L under continuous substitution, hypercalcemia up to 2.9 mmol/L (11.6 mg/dL) and hyperphosphatemia up to 2.5 mmol/L (7.7 mg/dL) were recorded. A histopathological study of the kidneys after death on day of life 14 revealed nothing but an unspecific glomerular swelling.



Supplementary Figure S2. Progression of renal function-indicating parameters during neonatal critical care in animals receiving placebo or UC-MSC as controlled infusion over 15 minutes. (**A**) Progression of the serum levels of creatinine and (**B**) urea. Every line represents the time course of one animal; three to seven valid measurements per animal and parameter were obtainable. The last valid creatinine measurements of an animal prior to day of life 14 are indicated with closed triangles (▼) as bilirubin and/or triglyceride levels interfered with the creatinine measurements after that time point. Temporal progression of the (**C**) urine output and (**D**) the specific urine gravity, both averaged over every 24-hour interval. Data is depicted as group mean (solid curves) with 95% confidence interval of the mean ($CI_{95\%}$; dotted curves). No significant ($P < 0.05$) differences between UC-MSC and placebo-receiving animals for any of the presented data, comparing data for every timepoint using Welch's two-sided, unequal variance *t*-test following Shapiro-Wilk testing and multiple testing adjustment by Šidák's correction.

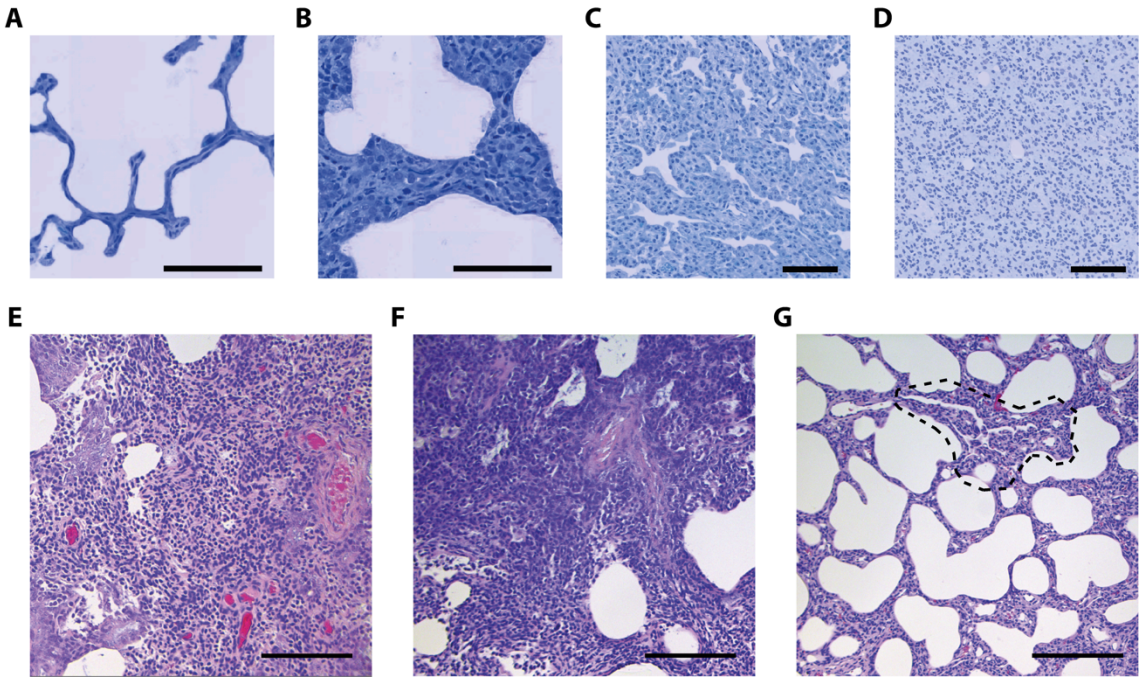


Supplementary Figure S3. Volume status during neonatal critical care in animals receiving placebo or UC-MSC as controlled infusion over 15 minutes. The (**A**) total fluid intake, depicted as group means (solid curves) and 95% confidence interval of the means (dotted curves). Comparing data for every twelve-hour interval using Welch's two-sided, unequal variance *t*-test following Shapiro-Wilk testing and multiple testing adjustment by Šidák's correction, the time periods with significant differences are indicated with a dashed box. Cohen's *d* was calculated based on pooled standard deviations. Analysis of the progression of (**B**) fluid balance, i.e. the difference between total fluid input and urine / stool discharge and (**C**) the relative change in weight from birthweight revealed no significant differences between groups.

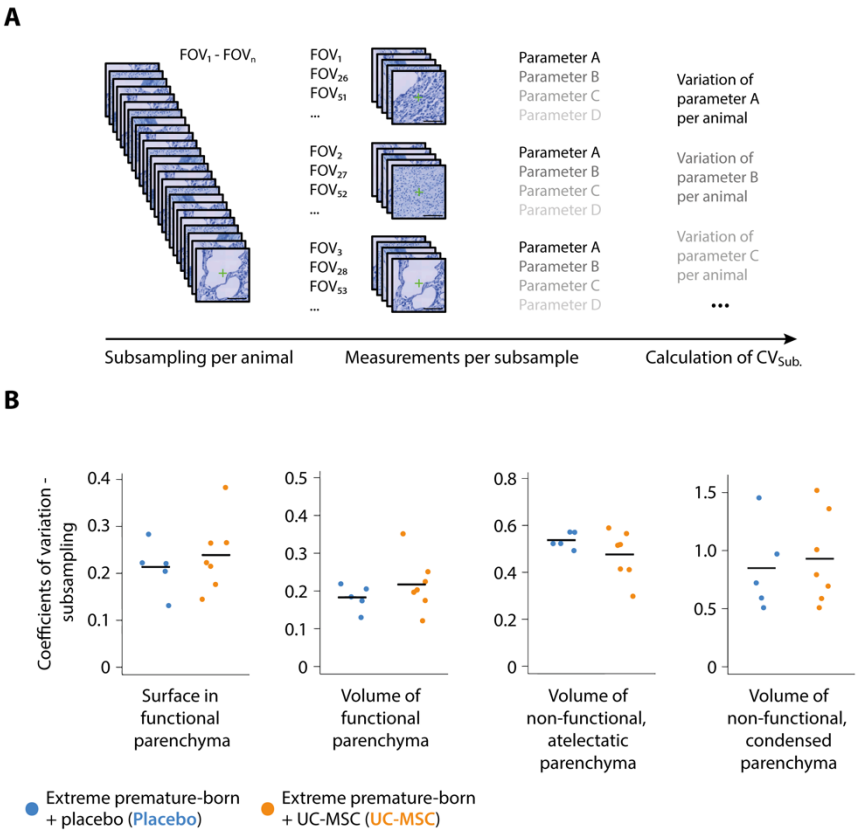


	Day of life 1	Day of life 7	Day of life 14
PIP / PEEP	21 / 5 cmH_2O	21 / 5 cmH_2O	18 / 5 cmH_2O
FiO_2	0.58	0.32	0.28
Respirator rate	28.0 min^{-1}	38.0 min^{-1}	25.7 min^{-1}
Oxygenation index	9.37	3.71	2.67
Ventilation index	25.82	35.24	20.17

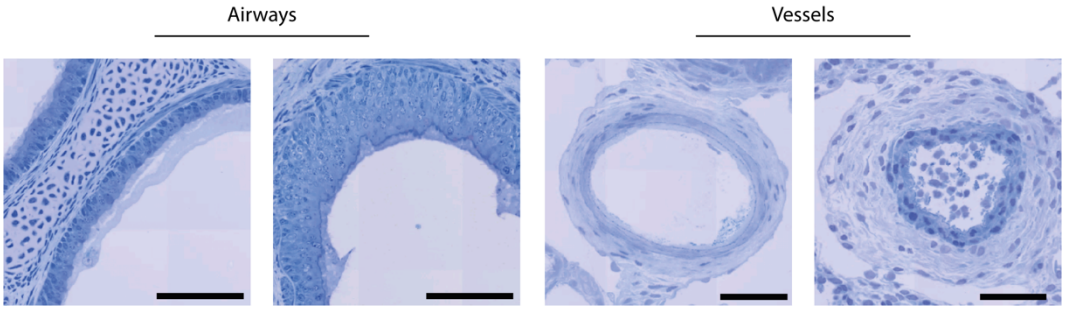
Supplementary Figure S4. Representative chest X-ray films from an extremely premature-born baboon (female, born after 124 days of gestation with 332 g birth weight) receiving UC-MSC. Abbreviations: PIP – positive inspiratory pressure, PEEP – positive end-expiratory pressure, FiO_2 – fraction of inspired oxygen. Width of the films approx. 7.5 cm.



Supplementary Figure S5. Representative photomicrographs of the functional (**A** and **B**) and the non-functional (**C** and **D**) pulmonary parenchyma in an extremely premature-born, ventilated lung fixed by perfusion. Staining toluidine blue on Technovit 7100. Morphology of the non-functional parenchyma in extremely premature-born lungs fixed by inflation with a liquid fixative. Note the absence of alveolar-like structures in the condensed lung areas shown in (**E**) and (**F**). Atelectasis was virtually absent in the inflation-fixed tissues; only a few small atelectatic lung areas were noted (encircled area in **G**). Staining haematoxylin and eosin on de-paraffinized slides. Scale bars 100 µm (**A**-**D**) or 200 µm (**E**-**G**).



Supplementary Figure S6. Analysis of spatial heterogeneity using subsampling of stereological data. (**A**) Schematic overview on the subsampling process. For every animal, the entire dataset of *n* FOV was separated into *m* = 25 systematic, uniform subsamples. Coefficients of variation were calculated based on the individual measurements per subsample. (**B**) Analysis of the spatial heterogeneity of the alveolar surface in ventilated animals receiving placebo or UC-MSC using subsampling techniques. Higher coefficients of variations indicate a more heterogenous distribution; no significant ($P < 0.05$) differences between groups using Welch's two-sided, unequal variance *t*-test following Shapiro-Wilk testing.



Supplementary Figure S7. Morphology of the non-parenchyma in extremely premature-born, ventilated lungs. Note the variability in airway and vascular/arteriolar wall appearance. Images derive from the lung of one animal; staining toluidine blue on Technovit 7100, Scale bars 100 µm.