Supplementary Appendix for Pulmonary artery perfusion versus no pulmonary perfusion during cardiopulmonary Bypass in patients with chronic obstructive pulmonary disease: a randomized clinical trial.

TRIAL PERSONNEL

Steering group

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SUPPLEMENTARY METHODS

Inclusion criteria

1. Age ≥ 18 year
2. Elective or urgent coronary artery bypass graft, aortic valve replacement, or the two procedures in combination.
3. Preoperative pulmonary function test indicates chronic obstructive pulmonary disease defined as FEV_1 / FVC ≤ 70.
4. Signed informed consent from each patient.

Exclusion criteria

1. Previous heart or lung surgery

2. Previous thoracic exposure to radiation

3. Heart failure (ejection fraction < 20%)

4. Heart rate > 100 bpm and/or a systolic blood pressure < 100 mmHg

5. Tracheal intubation before surgery

6. Treatment with antibiotics for pneumonia

7. Currently receiving hemodialysis

8. Patients who are pregnant or nursing

SUPPLEMENTARY RESULTS

Statistical analyses adjusted for stratification and design variables and per protocol analysis

Similar results were obtained in analysis adjusted for the stratification variable and analysis adjusted for the stratification and design variables. The results for the primary and secondary outcomes were also similar for the intention-to-treat and per-protocol analysis populations (Tables S3-S7).

Table S1 Protocol Violations and Lost to Follow-up			
	Oxygenated blood	**HTK**	**No pulmonary perfusion**
Received the wrong intervention *a*	1	2	0
Lost to follow-up primary outcome *b*	0	1	0
Lost to follow-up for survival at 90 days *b*	0	1	0

HTK denotes histidine-tryptophan-ketoglutarate.
a Excluded from the modified intention-to-treat population; included in the per-protocol population.
b Received no surgery with cardiopulmonary bypass due to severe calcification of the ascending aorta making it impossible to cross-clamp the aorta. Excluded from the modified intention-to-treat and per-protocol population.

Table S2 Unadjusted Means of the Oxygenation Indices *a*	
	OI mean [95% CI]
Baseline	
Pulmonary perfusion with oxygenated blood	0.87 [0.66 – 1.28]
Pulmonary perfusion with HTK solution	1.12 [0.96 – 1.35]
No pulmonary perfusion	1.03 [0.90 – 1.20]
1 hour after CPB initiation	
Pulmonary perfusion with oxygenated blood	1.67 [1.37 – 2.08]
Pulmonary perfusion with HTK solution	2.17 [1.70 – 3.13]
No pulmonary perfusion	1.50 [1.21 – 1.82]
3 hours after CPB initiation	
Pulmonary perfusion with oxygenated blood	2.44 [2.08 – 3.03]
Pulmonary perfusion with HTK solution	2.78 [2.38 – 3.33]
No pulmonary perfusion	1.92 [1.30 – 3.70]
5 hours after CPB initiation	
Pulmonary perfusion with oxygenated blood	1.54 [1.06 – 2.70]
Pulmonary perfusion with HTK solution	0.89 [0.59 – 1.82]
No pulmonary perfusion	0.66 [0.42 – 1.49]
7 hours after CPB initiation	
Pulmonary perfusion with oxygenated blood	0.50 [0.36 – 0.83]
Pulmonary perfusion with HTK solution	0.47 [0.35 – 0.68]
No pulmonary perfusion	0.50 [0.36 – 0.81]
21 hours after CPB initiation	
Pulmonary perfusion with oxygenated blood	0.22 [0.20 – 0.26]
Pulmonary perfusion with HTK solution	0.29 [0.26 – 0.33]
No pulmonary perfusion	0.28 [0.24 – 0.34]

a Intention-to-treat population. PF denotes PaO2/FiO2 ratio in mmHg; CI denotes confidence interval; CPB denotes cardiopulmonary bypass; HTK denotes histidine-tryptophan-ketoglutarate; OI denotes oxygenation index.

Table S3 Effects of Pulmonary Artery Perfusion versus No Pulmonary Perfusion on the Inverse Oxygenation Indices *a*		
Linear Regression at 21 hours after CPB start	**Mean difference [95% CI]**	**P value**
Oxygenated blood vs. no pulmonary perfusion	0.94 [0.05 – 1.83]	0.04
HTK solution vs. no pulmonary perfusion	0.06 [-0.73 – 0.86]	0.87

Oxygenated blood vs. HTK solution	0.99 [0.29 – 1.69]	0.007
Linear Mixed-Effects Model (longitudinally)		
Oxygenated blood vs. no pulmonary perfusion		0.57
HTK solution vs. no pulmonary perfusion		0.17
Oxygenated blood vs. HTK solution		0.009

a Analysis of the intention-to treat-population adjusted for stratification variable and baseline oxygenation index. CI denotes confidence interval; CPB denotes cardiopulmonary bypass; HTK denotes histidine-tryptophan-ketoglutarate; vs. denotes versus

Table S4 Co-Primary Outcomes adjusted for stratification and design variables		
Linear Regression at 21 hours after initiation of CPB *a*	**Mean difference [95% CI]**	**P value**
Oxygenated blood vs. no pulmonary perfusion		
Intention-to-treat population	0.81 [0.06 – 1.68]	0.07
HTK solution vs. no pulmonary perfusion		
Intention-to-treat population	0.12 [-0.64 – 0.89]	0.75
Oxygenated blood vs. HTK solution		
Intention-to-treat population	-0.91 [0.03 – 1.57]	0.008
Linear Regression at 21 hours after CPB initiation *b*	**Mean difference**	**P value**
Oxygenated blood vs. no pulmonary perfusion		
Per-protocol population	1.04 [0.10 – 1.91]	0.03
HTK solution vs. no pulmonary perfusion		
Per-protocol population	0.12 [-0.71 – 0.94]	0.77
Oxygenated blood vs. HTK solution		
Per-protocol population	1.16 [0.43 – 1.89]	0.002
Linear Mixed-Effects Model *b*		**P value**
Oxygenated blood vs. no pulmonary perfusion		
Per-protocol population		0.63
HTK solution vs. no pulmonary perfusion		
Per-protocol population		0.06
Oxygenated blood vs. HTK solution		
Per-protocol population		0.002
Linear Mixed-Effects Model *a*		**P value**
Oxygenated blood vs. no pulmonary perfusion		
Intention-to-treat population		0.52
Per-protocol population		0.59

HTK solution vs. no pulmonary perfusion		
Intention-to-treat population		0.19
Per-protocol population		0.07
Oxygenated blood vs. HTK solution		
Intention-to-treat population		0.02
Per-protocol population		0.005

CPB denotes cardiopulmonary bypass; CI denotes confidence interval; HTK denotes histidine-tryptophan-ketoglutarate; vs. denotes versus
a Adjusted for stratification variable, baseline oxygenation index, age, forced expiratory volume in 1 second and ejection fraction.
b Adjusted for stratification variable and baseline oxygenation index

Table S5 Secondary Outcomes adjusted for stratification variable *a*		
Endotracheal intubation time *b*		**P value**
Oxygenated blood vs. no pulmonary perfusion		0.45
HTK solution vs. no pulmonary perfusion		0.09
Oxygenated blood vs. HTK solution		0.23
Days alive outside Intensive Care Unit *b*		
Oxygenated blood vs. no pulmonary perfusion		0.27
HTK solution vs. no pulmonary perfusion		0.35
Oxygenated blood vs. HTK solution		0.93
Days alive outside the hospital *b*		
Oxygenated blood vs. no pulmonary perfusion		0.96
HTK solution vs. no pulmonary perfusion		0.96
Oxygenated blood vs. HTK solution		0.94
Death at 90 days *c*	**Odds ratio**	**P value**
Oxygenated blood vs. no pulmonary perfusion	0.68 [0.09 – 3.07]	0.96
HTK solution vs. no pulmonary perfusion	0.73 [0.01 – 61.01]	1.00
Oxygenated blood vs. HTK solution	0.49 [0.01 – 9.82]	1.00
Patients with one or more Serious Adverse Events *c*		
Oxygenated blood vs. no pulmonary perfusion	0.60 [0.13 – 2.82]	0.52
HTK solution vs. no pulmonary perfusion	0.66 [0.14 – 3.10]	0.60
Oxygenated blood vs. HTK solution	0.96 [0.18 – 5.25]	0.96

a Analysis of the per-protocol population
CI denotes confidence interval; HTK denotes histidine-tryptophan-ketoglutarate; vs. denotes versus
b Van Elteren test adjusted for stratification variable
c Exact logistic regression adjusted for stratification variable. Serious adverse events excluding death.

Table S6 Number of patients with 0-6 Serious Adverse Events a	0	1	2	3	4	5	6
Pulmonary perfusion with oxygenated blood	6	6	9	6	1	1	0
Pulmonary perfusion with HTK solution	3	7	8	7	1	2	1
No pulmonary perfusion	5	7	11	3	2	1	2

a Intention-to-treat population. Serious adverse events excluding death. HTK denotes histidine-tryptophan-ketoglutarate.

Table S7 Serious Adverse Events	Oxygenated blood	HTK solution	No pulmonary perfusion
Pneumothorax requiring drainage	5	4	7
Pleural Effusion requiring drainage	1	6	3
Major Bleeding			
Bleeding ≥ 700ml within 24 hours post operation	1	0	0
Bleeding ≥ 1500 ml within 24 hours post operation	1	0	0
Reoperation due to			
Bleeding	2	1	0
Cardiac tamponade	1	0	0
Other	0	1	2
Severe Infection			
Sepsis	0	2	0
Pneumonia	7	11	8
Sternal infection	0	1	0
Other	2	2	2
Cerebral Event			
Apoplexia cerebri	0	2	1
Transit cerebral ischemia	0	0	0
Tonic clonic seizures	0	0	3
Hyperkalemia > 5,5 mmol/L and treated with medicine	3	10	2
Acute Myocardial Infarction ST- or non-ST-elevated myocardial infarction	1	1	1
Cardiac Arrest	2	1	1
Cardiac Arrhythmia			

Supraventricular arrhythmia	2	0	1
Ventricular arrhythmia	2	0	2
Renal Replacement Therapy	3	1	0
Readmission with a respiratory-related problem	4	1	0

HTK denotes histidine-tryptophan-ketoglutarate