**Additional File 1**

**An Electrochemical Nitric Oxide Generator for In-home Inhalation Therapy in Pulmonary Artery Hypertension**

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**Table S1.** Gas composition produced from ENG.

**Table S2.** Based on the daily respiratory volume of adults, calculated amount of discharged VOC that may be inhaled within different 24 hours.

**Table S3.** Based on the daily respiratory volume of children, calculated amount of discharged VOC that may be inhaled within different 24 hours.

**Table S4.** Based on the daily respiratory volume of infants, calculated amount of discharged VOC that may be inhaled within different 24 hours.

**Table S5.** Based on the daily respiratory volume of the newborn, calculated amount of discharged VOC that may be inhaled within different 24 hours.

**Table S6.** Total amount of particulate matter emission from the ENG gas outlet in 24 hours.

**Table S7.** Preoperative blood routine, blood biochemistry and coagulation in vehicle group and MCT group.

**Table S8.** Preoperative arterial blood gas analysis in vehicle group and MCT group.

**Table S9.** Arterial blood gas analysis at 6 hours after NO inhalation in PAH group and PAH+NO group.

**Table S10.** Postoperative blood routine, blood biochemistry and coagulation in PAH group and PAH+NO group.

**Figure S1.** NO2 levels under a wider range of doses of NO (20-80ppm)

**Figure S2.** Real-world picture of the ENG working with continuous airway positive pressure (CPAP) mask for bedside inhalation.

**Table S1.** **Gas composition produced from ENG.**

|  |  |  |  |
| --- | --- | --- | --- |
| Test item | Unit | Detection limit | Results |
| N2 | % (v/v) | / | 99.91 |
| NO | 10-6 (v/v) | 5 | 1000 |
| NO2 | 10-6 (v/v) | 2.5 | ND |
| N2O | 10-6 (v/v) | 0.05 | ND |
| CO2 | 10-6 (v/v) | 0.05 | ND |
| O2 | 10-6 (v/v) | 0.01 | 4.30 |

N2, nitrogen; NO, nitric oxide; NO2, nitrogen dioxide; N2O, nitrous oxide; CO2, carbon dioxide; O2, oxygen; ND, not detected.

**Table S2.** **Based on the daily respiratory volume of adults, calculated amount of discharged VOC that may be inhaled within different 24 hours.**

|  |  |  |  |
| --- | --- | --- | --- |
| Compounds | Initial run  | 24 hours | 168 hours |
| Benzene | ＜40μg/d | ＜40μg/d | ＜40μg/d |
| Methylbenzene | ＜40μg/d | ＜40μg/d | ＜40μg/d |
| Ethylbenzene | ＜40μg/d | ＜40μg/d | ＜40μg/d |
| Paraxylene | ＜40μg/d | ＜40μg/d | ＜40μg/d |
| Meta-Xylene | ＜40μg/d | ＜40μg/d | ＜40μg/d |
| O-xylene | ＜40μg/d | ＜40μg/d | ＜40μg/d |
| Styrene | ＜40μg/d | ＜40μg/d | ＜40μg/d |
| Butyl acetate | ＜40μg/d | ＜40μg/d | ＜40μg/d |
| N-undecane | ＜40μg/d | ＜40μg/d | ＜40μg/d |
| Every other VOCs | ＜40μg/d | ＜40μg/d | ＜40μg/d |

VOC, volatile organic compounds.

**Table S3. Based on the daily respiratory volume of children, calculated amount of discharged VOC that may be inhaled within different 24 hours.**

|  |  |  |  |
| --- | --- | --- | --- |
| Compounds | Initial run |  24 hours | 168 hours |
| Benzene | ＜10μg/d | ＜10μg/d | ＜10μg/d |
| Methylbenzene | ＜10μg/d | ＜10μg/d | ＜10μg/d |
| Ethylbenzene | ＜10μg/d | ＜10μg/d | ＜10μg/d |
| Paraxylene | ＜10μg/d | ＜10μg/d | ＜10μg/d |
| Meta-Xylene | ＜10μg/d | ＜10μg/d | ＜10μg/d |
| O-xylene | ＜10μg/d | ＜10μg/d | ＜10μg/d |
| Styrene | ＜10μg/d | ＜10μg/d | ＜10μg/d |
| Butyl acetate | ＜10μg/d | ＜10μg/d | ＜10μg/d |
| N-undecane | ＜10μg/d | ＜10μg/d | ＜10μg/d |
| Every other VOCs | ＜10μg/d | ＜10μg/d | ＜10μg/d |

VOC, volatile organic compounds.

**Table S4. Based on the daily respiratory volume of infants, calculated amount of discharged VOC that may be inhaled within different 24 hours.**

|  |  |  |  |
| --- | --- | --- | --- |
| Compounds | Initial run | 24 hours | 168 hours |
| Benzene | ＜4μg/d | ＜4μg/d | ＜4μg/d |
| Methylbenzene | ＜4μg/d | ＜4μg/d | ＜4μg/d |
| Ethylbenzene | ＜4μg/d | ＜4μg/d | ＜4μg/d |
| Paraxylene | ＜4μg/d | ＜4μg/d | ＜4μg/d |
| Meta-Xylene | ＜4μg/d | ＜4μg/d | ＜4μg/d |
| O-xylene | ＜4μg/d | ＜4μg/d | ＜4μg/d |
| Styrene | ＜4μg/d | ＜4μg/d | ＜4μg/d |
| Butyl acetate | ＜4μg/d | ＜4μg/d | ＜4μg/d |
| N-undecane | ＜4μg/d | ＜4μg/d | ＜4μg/d |
| Every other VOCs | ＜4μg/d | ＜4μg/d | ＜4μg/d |

VOC, volatile organic compounds.

**Table S5. Based on the daily respiratory volume of the newborn, calculated amount of discharged VOC that may be inhaled within different 24 hours.**

|  |  |  |  |
| --- | --- | --- | --- |
| Compounds | Initial run  | 24 hours | 168 hours |
| Benzene | ＜0.42μg/d | ＜0.42μg/d | ＜0.42μg/d |
| Methylbenzene | ＜0.42μg/d | ＜0.42μg/d | ＜0.42μg/d |
| Ethylbenzene | ＜0.42μg/d | ＜0.42μg/d | ＜0.42μg/d |
| Paraxylene | ＜0.42μg/d | ＜0.42μg/d | ＜0.42μg/d |
| Meta-Xylene | ＜0.42μg/d | ＜0.42μg/d | ＜0.42μg/d |
| O-xylene | ＜0.42μg/d | ＜0.42μg/d | ＜0.42μg/d |
| Styrene | ＜0.42μg/d | ＜0.42μg/d | ＜0.42μg/d |
| Butyl acetate | ＜0.42μg/d | ＜0.42μg/d | ＜0.42μg/d |
| N-undecane | ＜0.42μg/d | ＜0.42μg/d | ＜0.42μg/d |
| Every other VOCs | ＜0.42μg/d | ＜0.42μg/d | ＜0.42μg/d |

VOC, volatile organic compounds.

**Table S6. Total amount of particulate matter emission from the ENG gas outlet in 24 hours.**

|  |  |
| --- | --- |
| Particle size range | Average concentration (μg/m3) |
| **First 8h** | **Second 8h** | **Third 8h** | **Total 24h** |
| ≤2.5 μm | ＜10 | ＜10 | ＜10 | ＜10 |
| ≤10 μm | ＜10 | ＜10 | ＜10 | ＜10 |

ENG, Electrochemical Nitric Oxide Generator.

**Table S7. Preoperative blood routine, blood biochemistry and coagulation in vehicle group and MCT group.**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Vehicle (n=6) | MCT (n=12) | *P* value |
| WBC (10^9/L) | 18.2±1.3 | 18.9±4.5 | 0.884 |
| RBC (10^12/L) | 6.2±1.0 | 7.4±0.3\* | 0.026 |
| HCT (%) | 28.5±3.3 | 33.9±3.7 | 0.050 |
| MCH (pg) | 14.4±0.9 | 14.4±1.0 | 0.999 |
| MCHC (%) | 309.3±17.5 | 312.7±9.1 | 0.693 |
| MCV (fl) | 46.3±3 | 45.9±3.5 | 0.839 |
| HGB (g/L) | 88.8±14.8 | 105.8±10.8 | 0.067 |
| RET (%) | 2.0±2.5 | 1.1±1.0 | 0.432 |
| PLT (10^9/L) | 680.5±185.1 | 706.3±148.2 | 0.812 |
| LYM (%) | 55.6±9.1 | 42.11±21.7 | 0.281 |
| Neutrophil (%) | 24.0±7.4 | 29.9±9.2 | 0.327 |
| TP (g/L) | 66.3±3.4 | 64.0±4.5 | 0.425 |
| ALB (g/L) | 28.1±4.3 | 28.1±2.7 | 0.999 |
| ALB/GLB | 0.75±0.19 | 0.8±0.14 | 0.645 |
| ALT (U/L) | 37.3±6.9 | 43.3±7.1 | 0.217 |
| AST (U/L) | 32.3±4.0 | 54.0±14.4\* | 0.027 |
| GGT (U/L) | 41.3±9.5 | 52.0±6.3 | 0.061 |
| UREA (mmol/L) | 2.1±0.5 | 1.9±0.6 | 0.663 |
| CRE (μmoI/L) | 57.4±15.1 | 52.45±6.9 | 0.493 |
| GLU (mmol/L) | 5.9±3.0 | 5.2±1.3 | 0.643 |
| PT (seconds) | 12.8±0.5 | 12.6±0.1 | 0.454 |
| APTT (seconds) | 22.0±3.2 | 32.7±9.5 | 0.073 |
| FIB (g/L) | 2.3±0.3 | 2.2±0.6 | 0.716 |

MCT, monocrotaline; WBC, white blood cell; RBC, red blood cell; HCT, hematocrit value; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; HGB, hemoglobin; RET, reticulocyte; PLT, platelet; LYM, lymphocyte; TP, total protein; ALB, albumin; GLB, globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; UREA, blood urea; CRE, creatinine; GLU, glucose; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, plasma fibrinogen; Data are mean ± SD; Statistical significance was determined using Student’s t-test (\**P* <0.05).

**Table S8. Preoperative arterial blood gas analysis in vehicle group and MCT group.**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Vehicle (n=6) | MCT (n=12) | P value |
| PH | 7.4±0.2 | 7.3±0.1 | 0.188 |
| PaO2 (mmHg) | 419.0±92.7 | 323.5±74.5\* | 0.031 |
| PaCO2 (mmHg) | 41.1±15.1 | 69.5±24.5\* | 0.026 |
| K+ (mmol/L) | 4.2±0.1 | 4.8±1.1 | 0.092 |
| Na+ (mmol/L) | 138.3±1.3 | 137.8±4.7 | 0.897 |
| Ca2+ (mmol/L) | 1.31±0.03 | 1.34±0.07 | 0.213 |
| Cl- (mmol/L) | 105.0±3.5 | 100.5±7.1 | 0.247 |
| SBE (mmol/L) | 1.9±2.8 | 3.5±4.0 | 0.373 |
| SB (mmol/L) | 28.0±1.0 | 27.4±3.1 | 0.499 |

MCT, monocrotaline; SBE, standard base excess; SB, standard bicarbonate; Data are mean ± SD; Statistical significance was determined using Student’s t-test (\**P* <0.05).

**Table S9. Arterial blood gas analysis at 6 hours after NO inhalation in PAH group and PAH+NO group.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **PAH (n=6)** | **PAH+NO (n=6)** | **P value** |
| PH | 7.4±0.3 | 7.4±0.2 | 0.955 |
| PaO2 (mmHg) | 319.3±117.7 | 461.7.8±74.0\* | 0.031 |
| PaCO2 (mmHg) | 48.8±11.0 | 38.9±6.3 | 0.086 |
| K+ (mmol/L) | 5.1±1.7 | 5.1±1.4 | 0.971 |
| Na+ (mmol/L) | 131.8±2.7 | 132.2±6.8 | 0.910 |
| Ca2+ (mmol/L) | 1.29±0.02 | 1.30±0.07 | 0.743 |
| Cl- (mmol/L) | 98.0±1.9 | 92.2±5.4 | 0.073 |
| SBE (mmol/L) | 4.8±1.3 | 10.7±1.9\* | 0.000 |
| SB (mmol/L) | 28.9±1.1 | 33.3±1.7\* | 0.003 |

PAH, pulmonary artery hypertension; NO, nitric oxide; SBE, standard base excess; SB, standard bicarbonate; Data are mean ± SD; Statistical significance was determined using Student’s t-test (\**P* <0.05).

**Table S10. Postoperative blood routine, blood biochemistry and coagulation in PAH group and PAH+NO group.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **PAH (n=6)** | **PAH+NO (n=6)** | **P value** |
| WBC (10^9/L) | 24.3±6.9 | 23.1±6.9 | 0.305 |
| RBC (10^12/L) | 6.8±0.6 | 7.5±1.7 | 0.788 |
| HCT (%) | 31.2±3.1 | 35.6±8.1 | 0.225 |
| MCH (pg) | 14.3±0.9 | 14.7±1.0 | 0.445 |
| MCHC (%) | 313.2±1.5 | 310.7±12.5 | 0.669 |
| MCV (fl) | 45.7±2.9 | 47.5±4.2 | 0.396 |
| HGB (g/L) | 97.7±9.5 | 111.0±25.7 | 0.248 |
| RET (%) | 0.6±0.5 | 0.7±0.6 | 0.851 |
| PLT (10^9/L) | 616.0±180.1 | 497.1±64.7 | 0.187 |
| LYM (%) | 35.3±6.5 | 35.8±8.5 | 0.901 |
| Neutrophil (%) | 49.5±10.1 | 48.7±10.5 | 0.887 |
| TP (g/L) | 65.0±3.6 | 67.2±5.9 | 0.451 |
| ALB (g/L) | 28.9±2.9 | 31.3±5.2 | 0.322 |
| ALB/GLB | 0.8±0.19 | 0.9±0.3 | 0.343 |
| ALT (U/L) | 73.6±23.2 | 73.7±20.3 | 0.777 |
| AST (U/L) | 209.3±128.4 | 174.4±122.6 | 0.790 |
| GGT (U/L) | 48.2±7.5 | 48.8±9.1 | 0.894 |
| UREA (mmol/L) | 3.0±1.0 | 3.7±1.6 | 0.419 |
| CRE (μmoI/L) | 54.0±8.2 | 49.7±7.5 | 0.301 |
| GLU (mmol/L) | 5.5±1.5 | 5.4±0.9 | 0.887 |
| PT (seconds) | 13.5±0.5 | 13.1±0.7 | 0.713 |
| APTT (seconds) | 38.9±9.9 | 33.0±12.2 | 0.480 |
| FIB (g/L) | 3.8±0.3 | 3.7±0.6 | 0.611 |

PAH, pulmonary artery hypertension; NO, nitric oxide; WBC, white blood cell; RBC, red blood cell; HCT, hematocrit value; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; HGB, hemoglobin; RET, reticulocyte; PLT, platelet; LYM, lymphocyte; TP, total protein; ALB, albumin; GLB, globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; UREA, blood urea; CRE, creatinine; GLU, glucose; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, plasma fibrinogen; Data are mean ± SD; Statistical significance was determined using Student’s t-test (\**P* <0.05).



**Figure S1.** NO2 levels under high dose of NO (20-80ppm)



**Figure S2.** Real-world picture of the ENG working with continuous airway positive pressure (CPAP) mask for bedside NO inhalation therapy.