

What is claimed is:

1. A method for maintaining the coupling of endothelial nitric oxide synthase (eNOS) to reduce the incidence or severity of cardiopulmonary bypass-induced pulmonary injury due to free radical formation in a patient during cardiopulmonary bypass comprising administering an effective amount of citrulline to the patient.
2. The method of claim 1, wherein the effective amount of citrulline is administered to the patient during or after the surgery.
3. The method of claim 1, wherein the effective amount of citrulline is administered to the patient during and after the surgery.
4. The method of claim 1, wherein the effective amount of citrulline is administered to the patient before, during, and after the surgery.
5. The method of any one of claims 1-4, wherein the effective amount of citrulline is an amount sufficient to reduce the uncoupling of endothelial nitric oxide synthase (eNOS).
6. The method of any one of claims 1-4, wherein the effective amount of citrulline is an amount sufficient to reduce the formation of free radicals.
7. The method of any one of claims 1-4, wherein the effective amount of citrulline is an amount sufficient to reduce the incidence or severity of cardiopulmonary bypass-induced pulmonary injury.
8. The method of any one of claims 1-7, wherein the citrulline is administered to the patient prior to the surgery.
9. The method of claim 8, wherein the citrulline is administered at about 12 hours prior to the surgery.
10. The method of any one of claims 1-9, wherein the citrulline is administered to the patient at the initiation of the surgery.
11. The method of any one of claims 1-9, wherein the citrulline is administered to the patient during the surgery.
12. The method of any one of claims 1-9, wherein the citrulline is administered to the patient after the surgery.
13. The method of any one of claims 1-12, wherein the surgery is to correct a cardiac defect.

14. The method of claim 13, wherein the cardiac defect is associated with excess pulmonary blood flow.
15. The method of claim 13, wherein the cardiac defect is an atrial septal defect.
16. The method of claim 15, wherein the atrial septal defect is a large arterial septal defect.
17. The method of claim 16 wherein the cardiac defect is a ventricular septal defect.
18. The method of claim 17, wherein the ventricular septal defect is a large unrestrictive ventricular septal defect (VSD).
19. The method of claim 13, wherein the cardiac defect is a single ventricle lesion.
20. The method of claim 19, wherein the single ventricle lesion is repaired by Glenn and Fontan procedures.
21. The method of claim 13, wherein the cardiac defect is Aortic Valve Stenosis (AVS), Atrial Septal Defect (ASD), Coarctation of the Aorta (CoA), Complete Atrioventricular Canal defect (CAVC), d-Transposition of the great arteries, Ebstein's Anomaly, I-transposition of the great arteries, Patent Ductus Arteriosus (PDA), Pulmonary Valve Stenosis, Single Ventricle Defects, Tetralogy of Fallot, Total Anomalous Pulmonary Venous Connection (TAPVC), Truncus Arteriosus, or Ventricular Septal Defect (VSD).
22. The method of any one of claims 1-21, wherein the surgery is arterial switch procedure.
23. The method of any one of claims 1-21, wherein the cardiopulmonary bypass is to repair a partial or complete atrioventricular septal defect (AVSD).
24. The method of any one of claims 1-21, wherein the cardiopulmonary bypass is to repair an ostium primum atrial septal defect (primum ASD).
25. The method of any one of claims 1-24, wherein the citrulline is administered at the initiation of the surgery is about 100–500 mg/kg of citrulline.
26. The method of claim 25, wherein the bolus of citrulline at the initiation of the surgery is about 100-300 mg/kg of citrulline.
27. The method of claim 26, wherein the bolus of citrulline at the initiation of the surgery is about 150 mg/kg of citrulline.
28. The method of claim 25, wherein the citrulline is administered at the initiation of the surgery is about 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg/kg of citrulline.

29. The method of any one of claims 1-28, wherein the citrulline administered during the surgery is added to the filtration.
30. The method of any one of claims 1-28, wherein the citrulline administered during the surgery is added to hemoconcentration replacement fluid.
31. The method of any one of claims 1-28, wherein the citrulline is added at about 100–500 $\mu\text{mol/L}$.
32. The method of claim 31, wherein the citrulline is added at about 100–300 $\mu\text{mol/L}$.
33. The method of claim 31, wherein the citrulline is added at about 100, 150, 200, 250, 300, 350, 400, 450, or 500 $\mu\text{mol/L}$.
34. The method of claim 33, wherein the citrulline is added at about 200 $\mu\text{mol/L}$.
35. The method of any one of claims 1-34, wherein a citrulline bolus is administered about 5-60 minutes after the surgery.
36. The method of claim 35, wherein a citrulline bolus is administered about 15-45 minutes after the surgery.
37. The method of claim 36, wherein the citrulline bolus is administered about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, or 60 minutes after the surgery.
38. The method of claim 36, wherein a citrulline bolus is administered about 30 minutes after the surgery.
39. The method of claim 35, wherein the citrulline bolus is about 5–50 mg/kg citrulline.
40. The method of claim 39, wherein the citrulline bolus is about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 mg/kg citrulline.
41. The method of claim 40, wherein the citrulline bolus is about 20 mg/kg citrulline.
42. The method of any one of claims 1-41, wherein a citrulline bolus is administered about 30 minutes after cardio pulmonary bypass decannulation.
43. The method of any one of claims 1-41, wherein citrulline is administered to the patient for about 12–48 hours after surgery.
44. The method of claim 43, wherein the citrulline is administered to the patient for about 12, 24, 36, or 48 hours after surgery.
45. The method of claim 43, wherein after surgery citrulline is infused into the patient for about 48 hours.

46. The method of claim 43, wherein the citrulline is administered by infusion at about 3–12 mg/kg/hour.
47. The method of claim 46, wherein the citrulline is administered by infusion at about 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 mg/kg/hour.
48. The method of claim 47, wherein the infusion is about 9 mg/kg/hour.
49. The method of any one of claims 1-48, wherein citrulline is administered intravenously.
50. The method of any one of claims 1-48, wherein citrulline is administered perioperatively.
51. The method of any one of claims 1-48, wherein a bolus of citrulline is administered at the beginning of the surgical procedure.
52. The method of any one of claims 1-51, wherein the citrulline is administered orally, intravenously, by inhalation, or a combination thereof.
53. The method of any one of claims 1-51, wherein the citrulline bolus is about 150 mg/kg.
54. The method of any one of claims 1-51, wherein the citrulline is added at about 200 $\mu\text{mol/L}$ to the filtration and hemoconcentration fluid utilized during the surgery.
55. The method of any one of claims 1-51, wherein a bolus of about 20 mg/kg of citrulline is administered after decannulation from cardiopulmonary bypass.
56. The method of any one of claims 1-51, wherein, after decannulation from cardiopulmonary bypass, a 9 mg/kg/hr continuous infusion of citrulline is administered, optionally for about 48 hours.
57. The method of any one of claims 1-56, wherein a bolus of 150 mg/kg of citrulline is administered at the beginning of surgery followed 4 hours postoperatively by a continuous infusion of 9 mg/kg/hour of citrulline.
58. The method of any one of claims 1-57, wherein the patient has a T1405N genotype in the CPSI gene of CC, AC, AA, or a combination thereof.
59. The method of claim 58, wherein the patient has a T1405N genotype in the CPSI gene of CC.
60. The method of any one of claims 1-57, wherein the patient's plasma citrulline level is raised above about 37, 50, 100, 150, or 200 $\mu\text{mol/L}$.
61. The method of any one of claims 1-57, wherein the patient's plasma citrulline level is raised above about 37, 50, 100, 150, or 200 $\mu\text{mol/L}$ postoperatively.

62. The method of any one of claims 1-57, wherein the patient's plasma citrulline level is raised above about 100 $\mu\text{mol/L}$.
63. The method of any one of claims 1-57, wherein the patient's plasma citrulline level is raised above about 100 $\mu\text{mol/L}$ postoperatively.
64. The method of any one of claims 1-57, wherein the patient's plasma citrulline level is raised to about 37–200 $\mu\text{mol/L}$ postoperatively, preferably 100–200 $\mu\text{mol/L}$ postoperatively.
65. The method of any one of claims 1-57, wherein the patient's plasma citrulline level is raised to about 37 $\mu\text{mol/L}$ to 2.5 mM.
66. The method of any one of claims 1-57, wherein the patient's plasma citrulline level is raised to between about 37 $\mu\text{mol/L}$ to 200 $\mu\text{mol/L}$, 100 $\mu\text{mol/L}$ to 1 mM/L, 150 $\mu\text{mol/L}$ to 500 $\mu\text{mol/L}$.
67. The method of any one of claims 1-66, wherein the patient's plasma citrulline level is raised for at least 12–48 hours postoperatively.
68. The method of any one of claims 1-66, wherein the patient's plasma citrulline level is raised for over 48 hours postoperatively.
69. The method of any one of claims 1-68, wherein the patient is a neonate, pre-adolescent, adolescent, or an adult.
70. The method of any one of claims 1-69, wherein the patient is less than about 6 years old.
71. The method of any one of claims 1-69, wherein the patient is less than about 10 days old.
72. The method of any one of claims 1-69, wherein the patient is a preterm infant.
73. The method of any one of claims 1-72, wherein the patient's intensive care unit (ICU) stay is decreased, preferably less than 27 days.
74. The method of any one of claims 1-73, wherein the patient is at risk for acute right-sided heart failure, tricuspid regurgitation, systemic hypotension, myocardial ischemia, and increased airway resistance.
75. The method of any one of claims 1-73, wherein the patient is at risk for persistent pulmonary hypertension of the newborn (PPHN).
76. The method of any one of claims 1-73, wherein the effective amount of citrulline is sufficient to prevent uncoupling of eNOS.
77. The method of any one of claims 1-76, wherein the patient is at risk for acute lung injury.

- 78. The method of any one of claims 1-76, wherein the patient is has acute lung injury.
- 79. The method of any one of claims 1-76, wherein the patient is at risk for postoperative pulmonary hypertension.
- 80. The method of any one of claims 1-79, wherein the patient has postoperative pulmonary hypertension.
- 81. The method of any one of claims 1-79, wherein the method reduces the incidence of sequelae of cardiopulmonary bypass-induced pulmonary injury in patients during cardiopulmonary bypass surgery and postoperatively.
- 82. The method of any one of claims 1-79, wherein the method reduces the severity of sequelae of cardiopulmonary bypass-induced pulmonary injury in patients during cardiopulmonary bypass surgery and postoperatively.