Table 1 Oxygen's Existence in the Blood

	Red Cells	Plasma
Arterial blood	19 ml × 50 × 1/5 = 190 ml	0.3 ml × 30 × 1/5 = 1.8 ml
Venous blood	14 ml × 50 × 4/5 = 560 ml	0.13 ml × 30 × 4/5 = 3.12
Total	750 ml	4.9 ml

Table 2 Carbon Dioxide Content in Blood

Carbon dioxide	Arterial blood	Venous blood
Pressure (mmHg)	40	46
In solution	3 ml/100 ml	3 + 0.5 = 3.5
Carbamino	3 ml/100 ml	3 + 0.7 = 3.7
Bicarbonate	42 ml/100 ml	42 + 2.8 = 44.8
Total	48 ml/100 ml	52

in the red cells. It is well known that when patients are subjected to hypovolemic shock, arteriovenous shunt formation occurs. The cellular components of the blood bypass the tissue perfusion and only the reduced flow of the plasma is perfused and supplies the needed oxygen to tissues. Thus, increasing the oxygen content in the plasma is extremely important. If the oxygen-carrying macromolecules containing even 5 to 8 ml of oxygen are infused, the oxygen supply to the tissues will be two times higher. This is easily achieved by infusing less than 100 ml of the oxygen-carrying macromolecular solution. Immediate and direct delivery of the needed oxygen to the tissues is achieved by this simple procedure. The capillaries should be opened and the shunt should be closed as a consequence. The normal tissue perfusion is established. Further oxygen supply to the tissues by red cells assures the functional recovery of organ function.

The availability of the oxygen-carrying macromolecules should change the traditional concept of blood transfusion.[5] It should be effective not only in the loss of the whole blood but also as a therapeutic agent for the treatment of various diseases induced by hypoxic tissues, including occlusive arterial diseases.

Hemoglobin as an Oxygen-Carrying Macromolecule

Stroma-free hemoglobin as an oxygen-carrying macromolecule is the obvious approach; however, it has two fundamental problems in being qualified as such.[7] First, it has a higher oxygen affinity (P_{50}) of 12–16 mmHg compared to that of the red cells having 26 mmHg. Secondly, its molecular weight (64,450 daltons) is too small and easily filterable through the glomerulus of the kidney. Thus, its vascular resisidence time is in the range of 2–4 hours. It produces hemoglobinuria and is considered to be toxic to the kidney.

Thus, many groups in the world have been trying to develop various types of hemoglobin preparations as artificial red cells. However, as described above, this author strongly believes that it should not be in the form of an oxygen-carrying particle but as an oxygen-carrying macromolecule.

Since 1977, this author's group together with Ajinomoto Co. in Japan developed a stabilized conjugated hemoglobin to eliminate the two negative aspects of the stroma-free hemoglobin while retaining the characteristics of oxygen-carrying macromolecules.[8–18] In order to normalize the oxygen affinity, pyridoxalated hemoglobin by pyridoxal 5 phosphate was generated. The polyoxyethylene conjugate increased the molecular weight of the hemoglobin up to 90,000 daltons. The resultant hemoglobin conjugate is shown in Fig. 5, Fig. 6, and Table 3. This stabilized hemoglobin (SHb) does not contain blood type antigens, pyrogen, or virus contamination. This freeze-dried stabilized hemoglobin's shelf life is over one year when it is stored at −80 °C. For its application, simply add distilled water, and the preparation can be infused after 0.2 μm filtration. Its plasma half life is 36 hours. The exchange transfusion of 80% plasma volume did not produce any mortality in

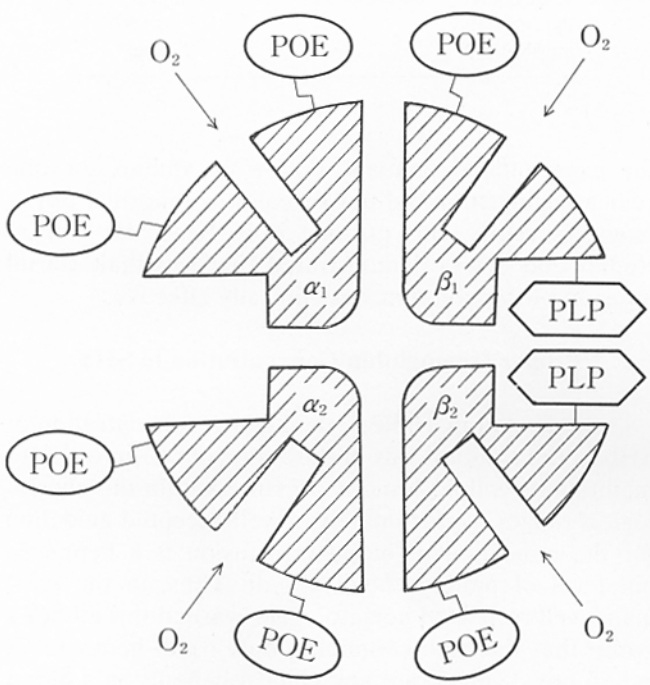

Fig. 5 Schematic structure of stabilized hemoglobin.