The theory and application of intravascular microbubbles as an ultra-effective means of transporting oxygen and other gases.

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Theoretically, volume-stabilized microbubbles may effectively support gas exchange between lungs and tissues[1]. Subcapillary sized bubbles can be generated by i.v. injection of an emulsion of dodecafluoropentane (DDFP, boiling temp 29°C). At body temperature, the DDFP particles evolve into bubbles initially composed of DDFP gas and then equilibrate with O_2 and CO_2 tensions in surrounding tissues. Thus, O_2 is transported from the lungs and CO_2 from the tissues. The feasibility of this method for life-sustaining oxygen supply has now been demonstrated in erythrocyte deprived normovolemic rats both anesthetized[2] (100% mortality in controls) and awake[3], in erythrocyte depleted normoxic pigs[4] and in treatment of severe experimental right-to-left shunts in pigs[3]. Injecting hematologically normal rats with DDFP emulsion provides for markedly increased tissue (muscle) O_2 tensions. In a separate study, potentially fatal hemorrhagic shock was induced in anesthetized pigs (n=8) by removing 50% of the blood volume. After bleeding, the systolic blood pressure was 71±2 mm Hg. Treatment animals (n=4) received 0.3 ml/kg of the DDFP emulsion and controls (n=4) received 0.3 ml/kg of blank. All the controls exhibited falling blood pressure and died in 67±39 (SE) min. By contrast, the systolic blood pressure in the treatment animals increased to above 100 mm Hg and three of the animals were euthanized after 6 hrs of post-treatment observation. One treatment animal became hypotensive after 3 hrs and died. On autopsy, the kidneys of this animal showed a large number of cysts and minimal normal tissue. Thus, i.v. administration of a 2% DDFP emulsion, in extremely small doses, may provide effective first-line treatment of hemorrhagic shock. In another study, the emulsion greatly enhanced the elimination of tissue nitrogen in O_2 breathing pigs[5]. This may have implications for the prevention and treatment of decompression sickness.

Extrapolating from the studies reviewed above, it appears that less than 1 ml of emulsified DDFP can provide for the O_2 consumption of a resting O_2 breathing adult person. The efficiency of the microbubbles for O_2 transport is underscored by the extremely small doses (0.002-0.014 ml/kg body weight) of DDFP, in the form of a 2% emulsion, which were used in these experimental studies.

REFERENCES

1. Van Liew H, Burkard M. Relationship of oxygen content to PO2 for stabilized bubbles in the circulation: theory. *J Appl Physiol* 1996; 81:500-508.
2. Tyssebotn I, Lundgren C, Bergoe G, Van Liew H, Goldinger J. Stabilized microbubbles as a blood substitute. *Undersea and Hyperbar Med* 1999; 26:96.
3. Tyssebotn I, Bergoe G, Goldinger J, Lundgren C. Dodecafluoropentane (DDFP) stabilized microbubbles support life without blood in awake rats. *Undersea and Hyperbaric Med* 1999; 26:97.

4. Tyssebotn I, Bergoe G, Lundgren C. Volume-stabilized intravascular microbubbles provide vital oxygenation in hemoglobin depleted pigs during "air breathing". *Undersea and Hyperbaric Med* 2001; 28:E30.
5. Lundgren C, Bergoe G, Tyssebotn I. Tissue denitrogenation by oxygen breathing is enhanced by perfluorocarbon-stabilized intravascular microbubbles. *Undersea and Hyperbaric Med* 2001; 28:E28.

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