Communication #324 from D. Radford Shanklin, Emeritus Professor, University of Tennessee, Memphis, and Library Reader, Marine Biological Laboratory, Woods Hole

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Format: PowerPoint Poster and Presentation converted to PDF with brief added remarks for clarification of the PPP frames and topical introduction

Background:

Experimental approaches to acute lung disorders in newborns require models replicated in large groups of animals, models which are adaptable to a variety of comparative situations. The issues which surround pulmonary oxygen toxicity are numerous and complex. Application of even clearly shown basic information derived from such models may not occur readily since clinicians follow Newton's laws of motion (*a body in motion tends to stay in motion...*), in medical parlance, practice patterns change slowly if at all. When oxygen is the center of the problem, the physiological concept of *hypoxemia/hypoxia* has become axiomatic. These studies have already challenged one axiom, the concept of partial pressure of gases in a mixture [*Lab.Invest.* 21:439-448, 1969]. Subsequent work challenged a second if generally unstated axiom, that the natural aerosphere, mostly oxygen and nitrogen, is the optimal adaptive state of mammalian lungs [*Biol.Neonat.* 20:140-158, 1972]. Neither of these basic biological principles has made their way into clinical practice. The current work, with oxygen at subatmospheric concentrations, is an even more profound challenge to the implied axiom of *hypoxia*. This is because they clearly demonstrate improved survival and less lung injury at the extreme low levels of oxygen, 3% and 7% at sea level pressures (1 A.T.A.).

Argon as prototype

Argon is ideal for molecular analysis of oxygen toxicity from the perspective of elemental or molecular characteristics. This is shown in the presentation in part through a comparison of the Lennard-Jones quantum-mechanical parameters: argon is very close to oxygen (page 2). Moreover, under appropriate conditions, argon greatly enhances survival in what is otherwise a steadily lethal model, with moderate precision as to the extent of lung injury.

The presentation

1. Title page and author disclaimer
2. Abstract from meeting program book
3. Lennard-Jones parameters and basic periodic table information about argon (Ar)
4. The animal model and the relationship between oxygen percentage and lung injury (from *Lab.Invest.* 21:439-448, 1969): pages 3 and 4
5. Experimental data, Figure 3: Comparative survival after bilateral cervical vagotomy in 3% oxygen in hydrogen, nitrogen, helium, sulfur hexafluoride, and ***argon***
6. Experimental data, Figure 4: Oxygen at 3% in nitrogen or hydrogen with and without vagotomy
7. Experimental data, Figure 5: Argon with and without vagotomy in 3% or 7% oxygen

ARGON AND THE PATHOPHYSIOLOGY OF PULMONARY OXYGEN TOXICITY

Radford Shanklin, M.D., F.R.S.M., Marine Biological Laboratory
(P.O. Box 511, Woods Hole, Massachusetts 02543)

The author has no interests to disclose

The Abstract

Radford Shanklin, M.D., F.R.S.M.
Marine Biological Laboratory
Woods Hole, Mass. 02543

Molecular interaction can be determined from biological experiments. In the case of dynamics at the atmosphere-lung interface the physicochemical and atomic attributes of inhalant gases has significant biological and pathogenetic consequences. Hyaline membrane disease (HMD) is a common and sometimes lethal disorder, especially in premature newborns. Current therapy includes artificial ventilation and increased oxygen in the inspired air, despite evidence the lesions can be induced by oxygen enrichment [*Lab.Invest.* 21:439, 1969]. Bilateral cervical vagotomy (BCV) is a standard method of inducing ventilatory distress which leads to HMD [*J.Exp.Med.* 66:397, 1937; *Biol.Neonat.* 6:340, 1964; *Biol.Neonat.* 11:61, 1967]. The lungs of post-vagotomy newborn rabbits show the lesions of HMD in extent directly proportionate to the percentage of oxygen in polybaric (0.2 - 3.0 Atm.Abs) mixtures with nitrogen. Avery [*Pediatrics* 32:801, 1963] found that lesions of HMD did not form at very low levels of oxygen (3-4% in nitrogen) in various newborn animals, suggesting that inhalant hypoxia was not a pathogenetic factor *per se*. The observation of lung injury proportionate to oxygen percentage indicates the physiological axiom of gas effects by their partial pressure is an artefact of sea level gas dynamics. The toxic effect of oxygen can be viewed as nitrogen lack. Some lung injury does occur when only 3 and 7 per cent oxygen in nitrogen is used, suggesting rather a specific oxygen effect. When nitrogen is replaced by hydrogen, helium, neon, argon, or sulfur hexafluoride, the extent of lesions often increases, indicating again a fundamental oxygen-nitrogen interaction. Low level studies with hydrogen and argon are especially instructive with and without BCV: (1) extremely long survival without BCV in oxygen-argon at 3% and 7 %; (2) significant but less enhancement of survival in 3% oxygen-hydrogen; (3) no distinction in survival after BCV for 3% oxygen in nitrogen or hydrogen; (4) a pattern of lesion formation in the alternative gas mixtures which suggests nitrogen has a partially protective effect along with its stochastic competition for a common oxygen-nitrogen receptor or transmembrane port; and (5) generally, the mammalian lung is well adapted by evolution to current atmospheric composition but at the price of more inhaled oxygen than is required for cellular function [*Perspect.Biol.Med.* 13:80, 1969], allowing for toxic effects. The distinctions amongst these gases in the biologic sense are due to differences in their mass, monoatomic or diatomic structure, possibly viscosity in air passageway flow, inherent energy state, and at low levels, in the electron saturation of the outer atomic shell. Unbuffered oxygen enrichment of air for ventilatory support is fundamentally injurious; hydrogen has obvious risks in a clinical setting but argon, which is abundant, non-flammable, and relatively non-toxic, may be the diluent gas of choice for ventilatory support.

Cite as: 42nd Annual Meeting, Middle Atlantic Region, American Chemical Society, May 21-24, 2011, University of Maryland, College Park, abstract 415, p. 262

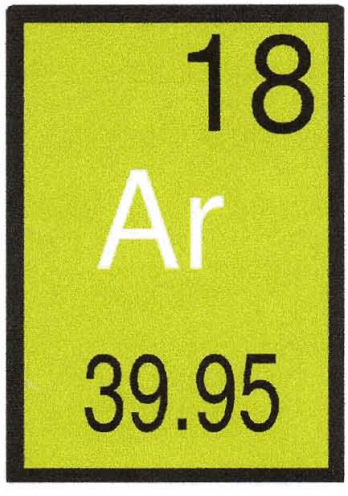
By invitation of the program general chairman, Michael P. Doyle, Ph.D., Chemical Society of Washington

Argon – The *Lazy* Atom, is similar to oxygen per the Lennard-Jones parameters:

Argon is 0.93% of the atmosphere of the earth by volume

Molecule	ε/k, °K	r^*, Å	r_0, Å
N_2	95.05	1.151	3.698
O_2	118	3.88	3.46
Ar	110.8	3.822	3.405

Hill, TL, *An introduction to statistical mechanics*, 1960 p. 484.



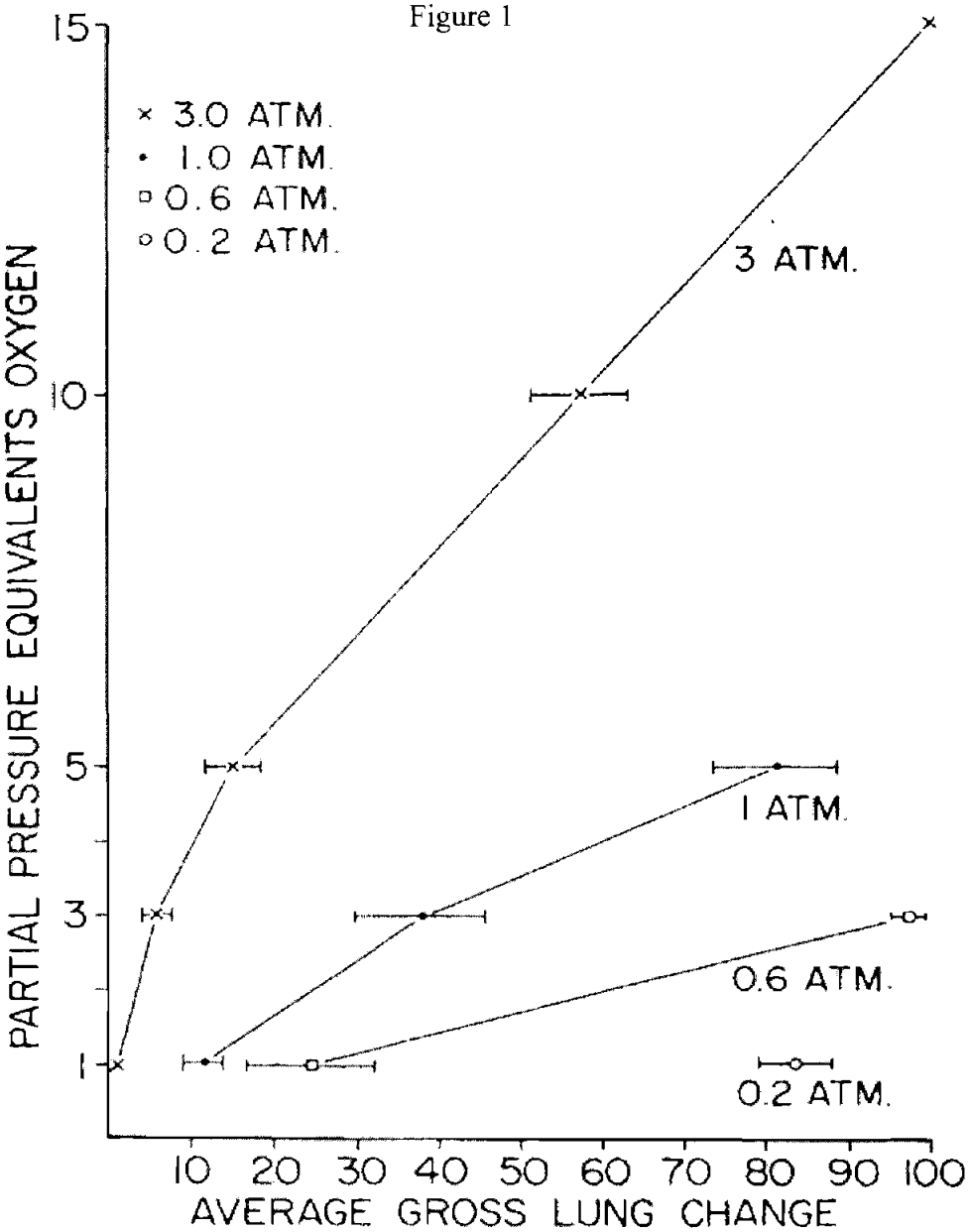
The Model

Bilateral cervical vagotomy causes ventilatory distress in newborn rabbits [Exp.Mol.Pathol. 2010, 89:36-45]. The resulting lung lesion depends on the amount of oxygen →→ **Figures 1 and 2**

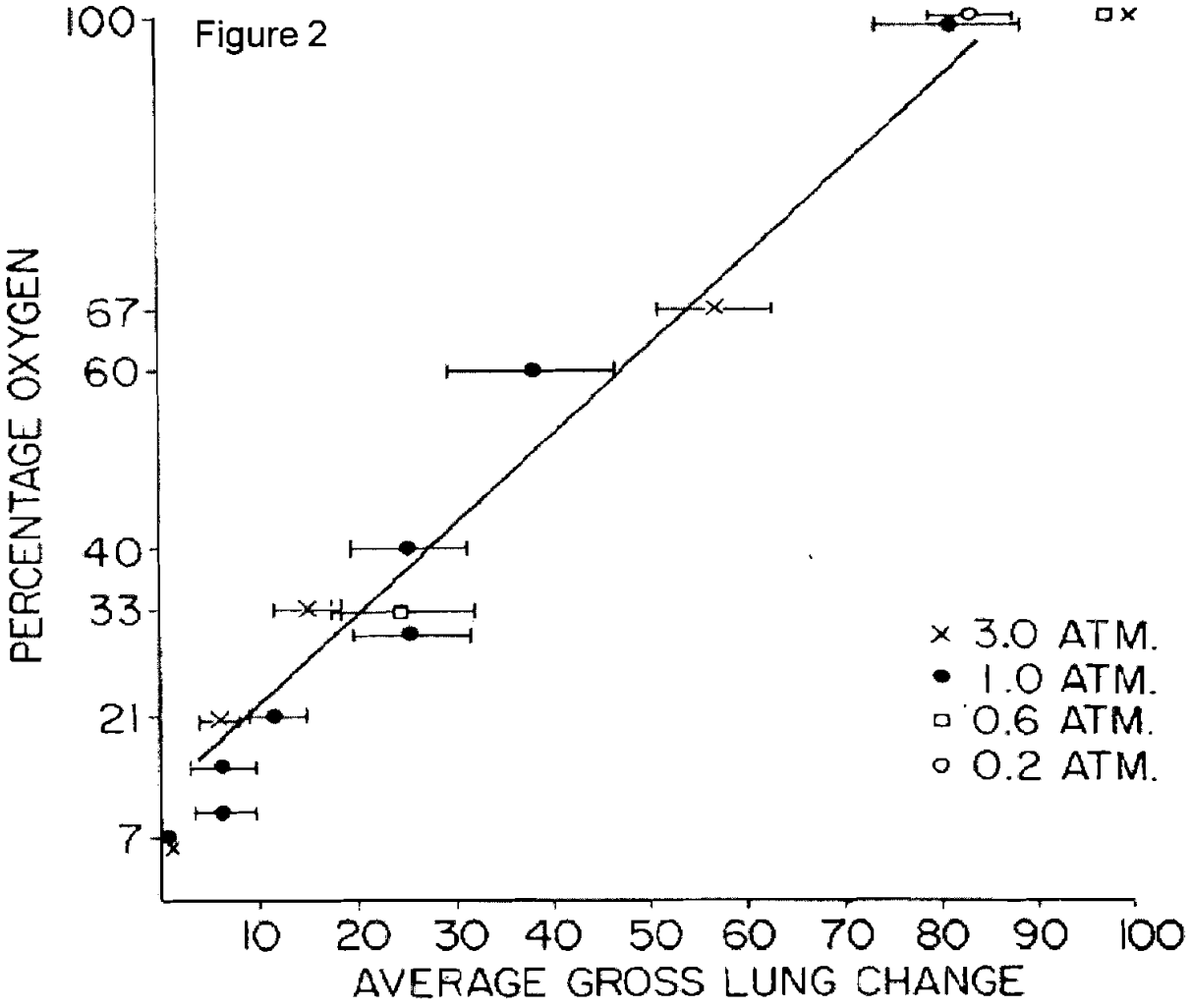
The Problem

The principle of gas effect according to its partial pressure is an artefact of sea level physiology. When the oxygen- nitrogen mixture of which air is the *baseline* of respiratory therapy, is changed by oxygen enrichment, it overrides the protective effect of nitrogen. Ventilatory distress induced by BCV reveals the injury effect is due to oxygen percentage composition and not by partial pressure:

Figure 1



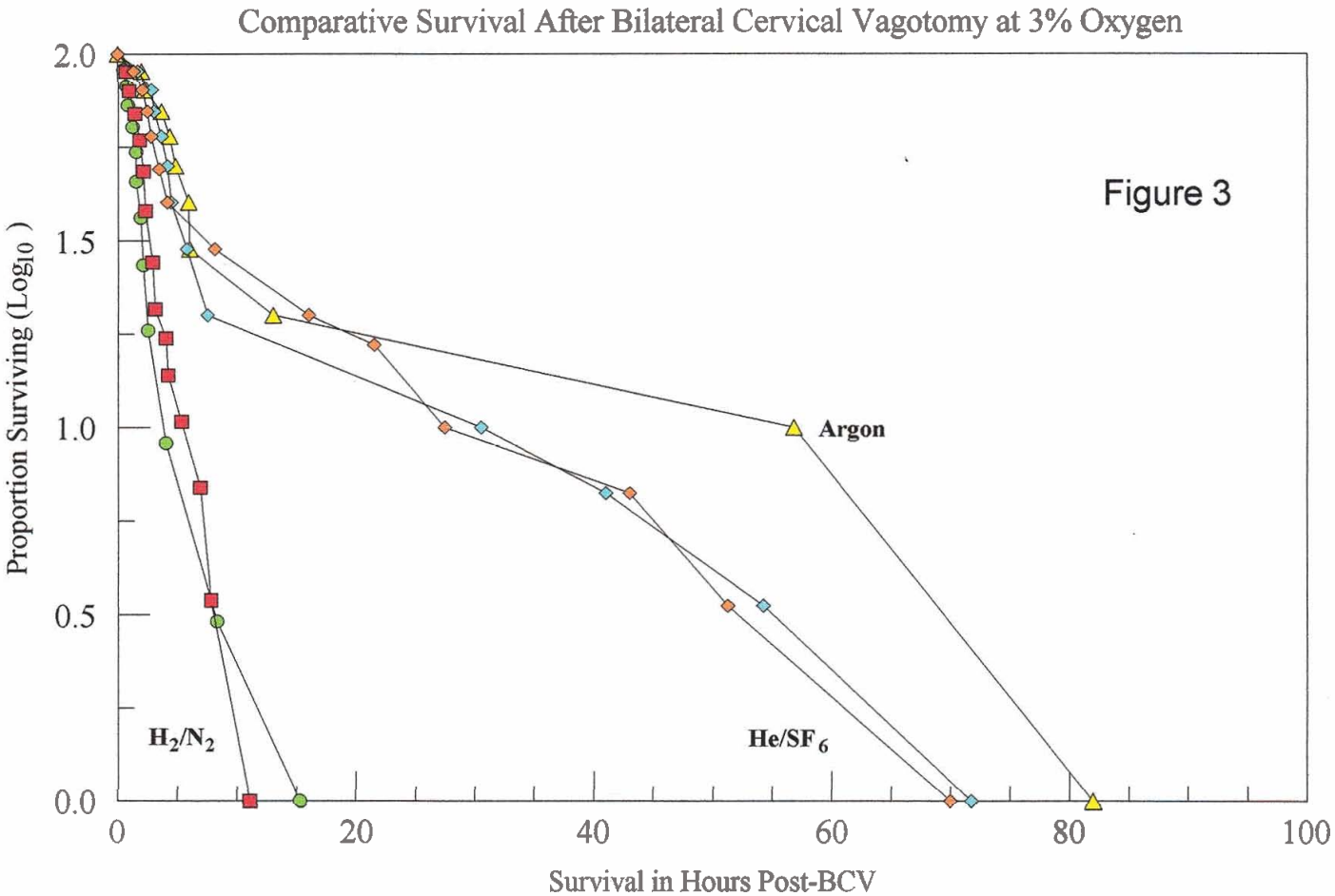
. Relationship of oxygen by partial pressure equivalent (*PPE*) to lung lesions. The limits of mean ± standard error of the mean have been omitted for clarity on this point: 3.0 atm. abs., 1 *PPE* (0.5 ± 0.7 per cent). The point 3.0 atm. abs., 15 *PPE* is unique (100 ± 0.0 per cent).



Relationship of oxygen by percentage to lung lesions. The limits of mean ± standard error of the mean have been omitted for clarity on these points: (1) 0.6 atm. abs., 100 per cent oxygen (97.2 ± 2.2 per cent); (2) 1.0 atm. abs., 7 per cent oxygen (0.2 ± 0.2 per cent); and (3) 3.0 atm. abs., 7 per cent oxygen (0.5 ± 0.7 per cent). The point 3.0 atm. abs., 100 per cent oxygen is unique (100 ± 0.0 per cent).

The Experimental Data

Figure 3: 3% oxygen is intuitively toxic, a severe level of inhalant hypoxia but from the established principle of oxygen:nitrogen competition at the air:lung interface (the terminal air spaces) the replacement of nitrogen by other diluents has profound effects, previously shown in 1972 for oxygen 20-100% [*Biol.Neonate* 20:140-158] , is also true for low levels of oxygen.



The five survival plots aggregate in an interesting manner. Firstly, argon stands alone with a distinctive prolonged shoulder. Secondly, the two diatomic gases, nitrogen and hydrogen, closely track each other. Finally, the seemingly very different helium and sulfur hexafluoride, also track together very closely. Though SF_6 has octagonal form, it is tightly bound and likely presents to the air:lung interface as a spheroidal molecule, just like helium. The diatomic gases mimic the similar profile of oxygen, blocking oxygen uptake at the entry limiting plane of pulmonary structure prior to the binding sink of circulating hemoglobin in erythrocytes.

The Experimental Data

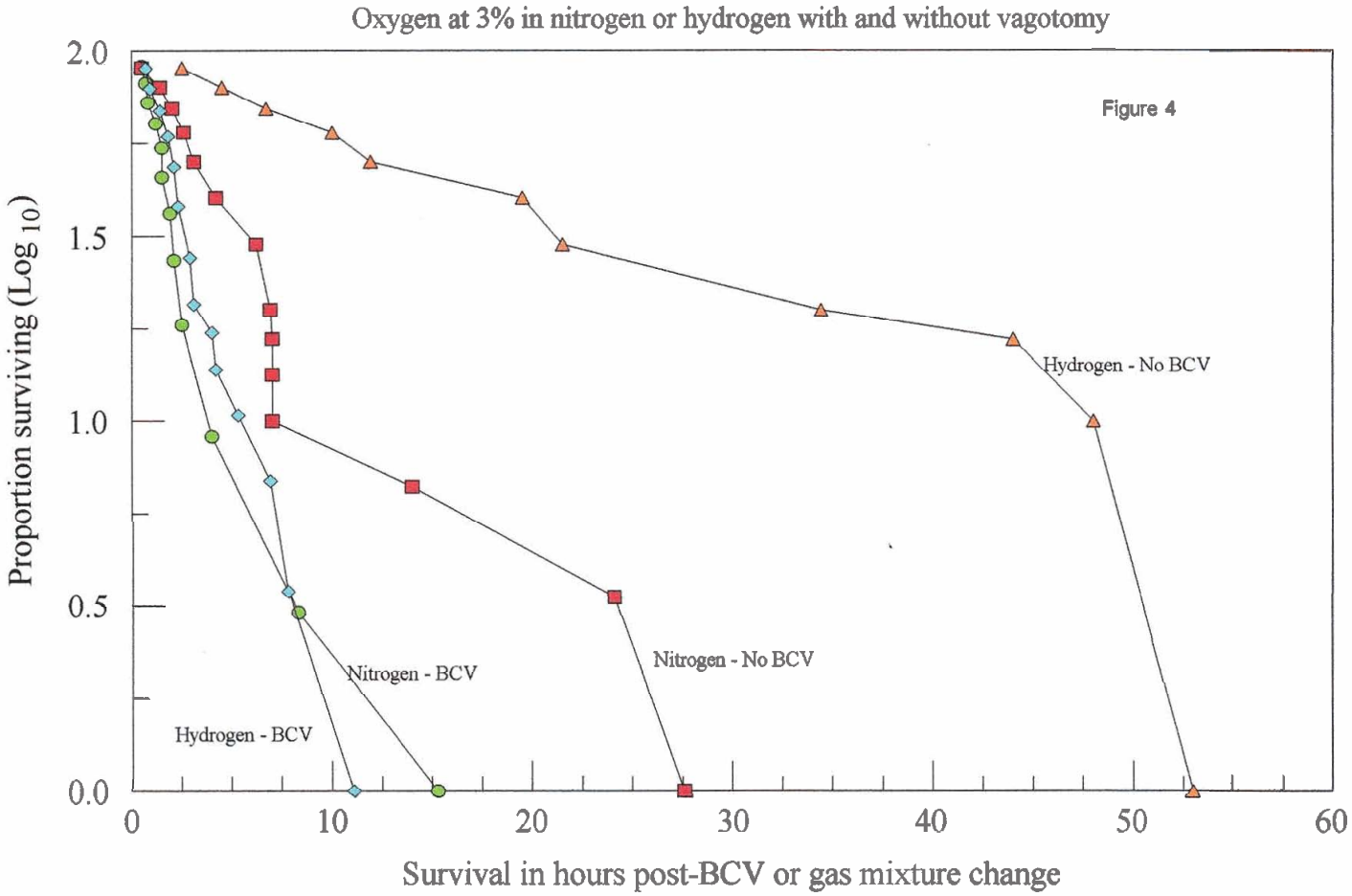
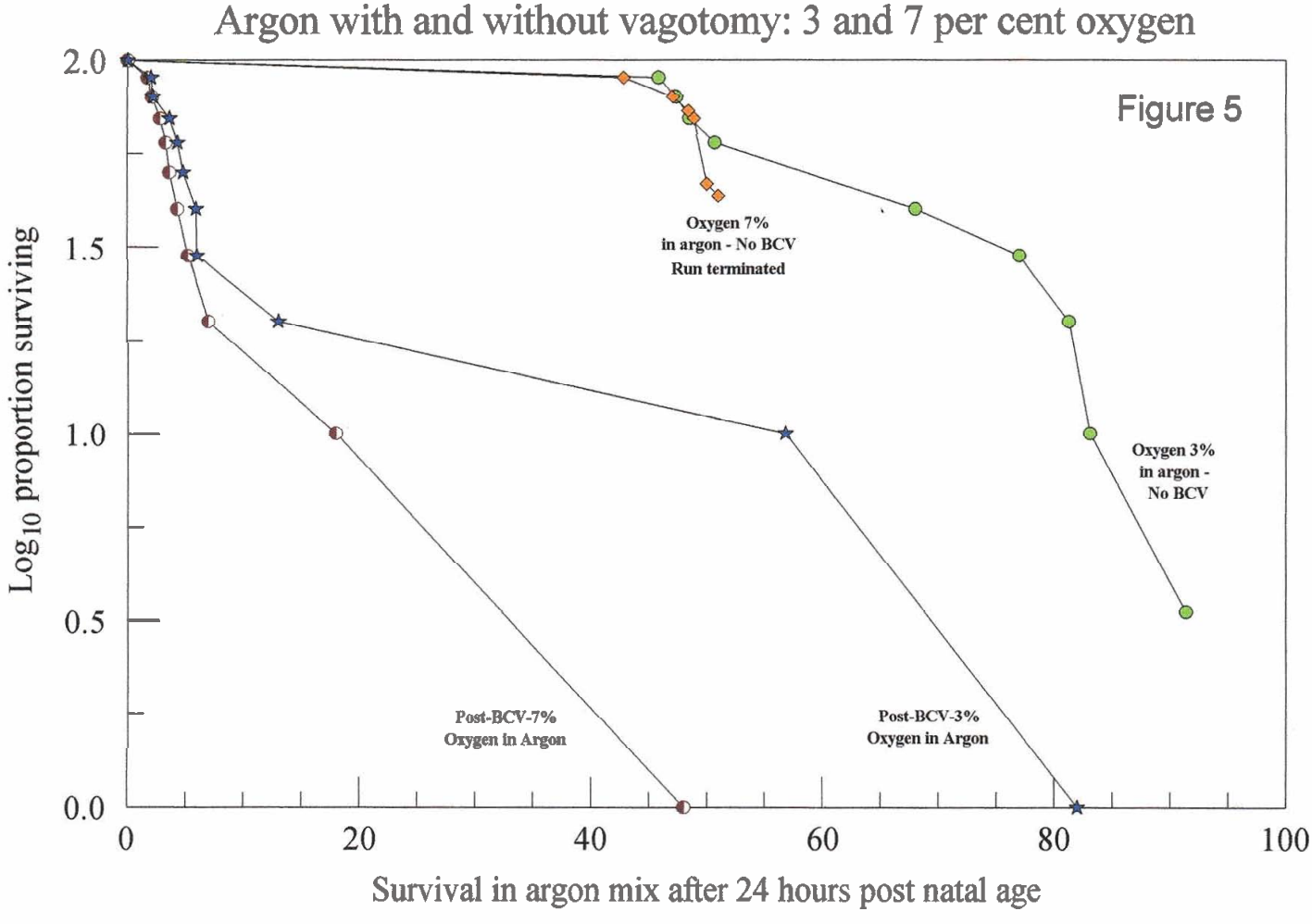


Figure 4: 3% oxygen in nitrogen or hydrogen without BCV yields better survival than after BCV (to the left) but not as well as argon (Figure 5). This comparative plot brings into focus the special relationship between oxygen and nitrogen referent the receptivity of the entry limiting plane. For operational purposes this will be provisionally identified as the outer cell membrane of lung epithelium, mainly type 1 pneumocytes from their overwhelming numbers at the air:lung interface, modulated by the content of the aqueous lung lining layer. The paired post-vagotomy nitrogen and hydrogen plots are of course the same as in Figure 3. The considerable contribution of induced ventilatory distress is also quite clear. The area under the curve (AUC) for both post-BCV gas mixtures are about equal and roughly half that for 3% O_2 in nitrogen without BCV. And, in turn, the AUC for hydrogen-no BCV is three times that for nitrogen-no BCV. Although H_2 is diatomic like N_2, it is a much smaller molecule and does not block oxygen as effectively. Thus, the injury reaction of the lung to oxygen depends in part on the atomic characteristics of the outer electron shell or orbit of oxygen and the various diluent gases used in these experiments.

The Experimental Data

Figure 5: 3% oxygen in argon after BCV yields better survival than 7% oxygen after BCV. The 7% oxygen run without vagotomy was terminated after 50 hours since the survival in the two groups (3% and 7%) was the same up to that point. This graph indirectly supports an interpretation that as more oxygen is supplied the greater the injury becomes, here in a reduced survival. The AUC for 3% O_2 post-BCV is more than twice that for 7% O_2.



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