Efficacy of Oxygen Enriched Gas Mixtures in the Treatment of Acute Myocardial Infarction

In this issue, Maroko and associates report evidence, obtained from experiments in dogs, that a well tolerated increase in the inspired concentration of oxygen (40%) reduces acute myocardial ischemic injury significantly. Differences were striking when compared to animals breathing the normal room air concentration of oxygen (≈ 21%) and studied in an otherwise identical manner. In another group of dogs, exposure to 100% O₂, a level known to produce pulmonary damage if continued for long periods of time, was not associated with additional improvement when compared to the group breathing 40% O₂.

This experimental demonstration of partial protection from ischemic myocardial injury, in association with a simple benign intervention, poses an important question to the physician concerned with the serious and sometimes fatal human counterpart, acute myocardial infarction. Will prompt continuous treatment with 40% oxygen be beneficial in patients suffering from acute ischemic myocardial injury? In order to analyze this question critically, the relevant assumptions and potential mechanisms for benefit must be explored critically.

Assumptions Pertinent to Resuscitation of Ischemic Myocardial Cells

The first assumption, that acute myocardial infarction in man is associated with hypoxic injury, can be answered affirmatively. Ischemia and induction of transmural anaerobic metabolism have been demonstrated unequivocally, after occlusion of a coronary artery.¹

Reduction of myocardial injury, as a consequence of a higher Po₂ in arterial blood (PaO₂), in comparison to what would occur in the unmodified situation, implies that in the ischemic region some cells remain viable for a sufficiently long interval that successful clinical intervention is practical. Such an interval should be at least several hours in length; survival for 24 or 48 hours would increase the size of the potential population to be benefited dramatically, since active treatment is often delayed. Survival of ischemic myocardial cells for some hours is thought likely.²

Under diverse experimental circumstances the extent of myocardial injury after occlusion has been modified, supporting the common assumption that some myocardial cells remain viable (that would otherwise die) in the ischemic region.³

Evidence that this is so in the clinical setting is lacking. There is indirect evidence from observations of patients suffering from acute cerebral ischemic episodes, however, that nonfunctioning regions of brain remain viable for a period of hours; exposure to hyperbaric oxygen will cause a reversal of the neurologic deficit in a significant fraction of these patients during a several-hour interval after onset of clinical symptoms.⁴

The next assumption to be tested is that a modest increment in the PaO₂ can maintain viability of myocardial cells that would die otherwise within a short period of time. The evidence presented by Maroko et al. is persuasive. Amelioration of epicardial injury currents, although not translatable directly, is clearly consistent with reduced injury. The paired observations of reduced histologic damage and higher

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maintained levels of creatine phosphokinase in affected regions provides good support for this interpretation. That a modest increment in $P_{\text{Pn}}$ can preserve viability of myocardial cells within an ischemic zone has yet to be demonstrated in man, however.

Preservation of some viable myocardial cells within an ischemic zone during a 24 hour period by breathing 40% $O_2$ is only a temporary accomplishment in itself. To be useful clinically, this "therapeutic lifeboat" must be followed within a few days by the development of collateral arterial vessels, providing sufficient perfusion to sustain metabolic requirements of the remaining viable cells in the zone of injury. Collateral vessels develop in animal models within four days after ischemic injury to the myocardium. While similar collaterals develop in man, the time course is unknown. Also we do not know how therapeutic intervention with an oxygen enriched breathing gas affects the rate of collateral vessel development. The latter question can be answered directly in animals and is clearly important.

Mechanisms for Benefit to be Derived from Oxygen

Systematic analysis of oxygen therapy in the treatment of acute myocardial infarction requires assessment of potential mechanisms for benefit.

Clearly, an increase in $O_2$ content and transport by arterial blood, accompanying breathing of 40% oxygen, cannot explain reduced myocardial injury. In the experiment reported, the increment in $P_{\text{O}_2}$ of 100 mm Hg would be accompanied by addition of only 0.5 vol% $O_2$ in physical solution. Only correction of marked hemoglobin $O_2$ unsaturation would alter content and transport significantly. This was not the case in this experiment nor is significant arterial hemoglobin unsaturation common in acute myocardial infarction.

The modest increase in $P_{\text{O}_2}$ does provide a more favorable gradient for passive diffusion of $O_2$ from capillary blood to the recipient myocardial cell. There are severe biophysical limitations to transfer of $O_2$ by diffusion, however. Poor solubility of $O_2$ and a high level of consumption by the myocardium limit the finite intercapillary distance for adequate $O_2$ transfer by diffusion to a very small distance. These formidable theoretical constraints upon adequate oxygen delivery via passive diffusion have been supported by many studies, even under circumstances where the $P_{\text{O}_2}$ has been increased well above 1000 mm Hg in a hyperbaric chamber. It also seems likely that, if an improved gradient of $P_{\text{O}_2}$ were significant in the experiment reported by Maroko, additional improvement would have been observed when the breathing gas was 100% $O_2$. Nevertheless, some gain via improved passive diffusion from a higher $P_{\text{O}_2}$ level through a broad heterogeneous band of ischemia to needy myocardial cells is a possibility that cannot be ruled out at this juncture.

A reduction in oxygen demand by tissues would be a plausible and beneficial consequence of increasing the $P_{\text{O}_2}$. Since myocardial injury is associated with depressed or absent contractility of cardiac muscle, a state in which $O_2$ consumption is at a minimum, improvement due to this mechanism seems unlikely.

An increase in total peripheral resistance due to the pharmacologic action of oxygen might lead to improved perfusion of the heart. In this experiment, however, there was no evidence that the modest increment in $O_2$ affected peripheral resistance significantly. At a somewhat comparable level of $P_{\text{O}_2}$, in exercising man, no change in heart rate was noted, suggesting that the systemic vascular effects, noted when breathing pure oxygen, are not present breathing 40% oxygen.

The most plausible explanation by the authors for their findings is that the increased $P_{\text{O}_2}$ was associated with improved microperfusion of ischemic myocardium because blood was diverted away from better perfused regions of the heart. The resultant increase in the pressure gradient between the normal and ischemic area is an attractive hypothesis both because other explanations are less than convincing and because the diversion of blood to ischemic myocardium would supply other needed substrates in addition to oxygen. Also, improved perfusion would provide sufficient volume flow of blood to carry off toxic metabolites from the injured cells.

The failure of 100% oxygen to provide additional benefit, when compared to findings breathing 40% oxygen, can be explained in diverse ways. Further widening of the $P_{\text{O}_2}$ gradient may fail to reduce injury further because diffusive conduction of $O_2$ molecules is ineffective when intercapillary distances are increased. Also, an additional increase of the $P_{\text{O}_2}$ is not associated with a major increase in $O_2$ content in transport by arterial blood, for reasons reviewed above. Therefore, no large gain in bulk transport of $O_2$ is attained. If an increased pressure gradient between well perfused and poorly perfused hypoxic myocardium is attained when breathing 40% $O_2$, this response may be maximal already and no further gain would occur when breathing 100% oxygen. Another explanation is that breathing 100% oxygen lowers systemic blood flow sufficiently, as has been demonstrated heretofore, so that bulk $O_2$ delivery to the heart is not significantly different in comparison to the findings when breathing 40% oxygen. Under these circumstances a similar $O_2$ delivery would be associated in all probability with identical myocardial consequences.
Conclusion

This review raises a series of questions concerning the mechanisms by which the breathing of 40% \( \text{O}_2 \) reduces myocardial injury in experimental models and the parameters that would determine whether reasonable clinical benefit could be attained. Clearly, questions concerning altered distribution of blood flow within the heart and the development of collateral circulation under these considerations merit serious study in laboratory models. In view of the benign nature of therapeutic intervention with 40% oxygen and the extensive background of data indicating that this level is well tolerated for substantial periods of time,\(^1\) a controlled therapeutic trial in man appears warranted. In as diverse a population as that represented by man suffering from acute myocardial infarction, however, selection criteria, controls and methods of study must be considered and implemented with great care if meaningful results are to be obtained.

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_Circulation._ 1975;52:357-359
doi: 10.1161/01.CIR.52.3.357

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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