Pulmonary hypertension in chronic obstructive pulmonary disease: the right ventricular hypothesis.

D A Morrison

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Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease:

The Right Ventricular Hypothesis

Yet nature desiring that the blood should be strained through the lungs, was forc'd to add the right ventricle, by whose pulse the blood should be forc'd through the very lungs out of the vena cava into the receptacle of the left ventricle . . .

William Harvey, 1628
Exercitatio Anatomica de
Motu Cordis et Sanguinis in Animalibus

Pulmonary hypertension is an important determinant of the quantity and quality of life in patients with chronic obstructive pulmonary disease (COPD). The mortal significance of pulmonary hypertension in COPD patients has been demonstrated repeatedly.[1-2] Among selected patients, low flow oxygen can interrupt this process of decline and death.[3-4] The study by Ashutosh and coworkers in this issue of *Chest* (see page 393) extends these findings. These workers have again identified pulmonary hypertension as a bad prognostic sign and the relief of pulmonary hypertension with oxygen as a good prognostic sign.

For most patients with cardiopulmonary disorders, the major determinant of quality of life is exercise tolerance. Moderate to severe elevations in exercise pulmonary pressures among patients with COPD have been confirmed repeatedly.[2,5] Here also, it has been observed that in selected patients, oxygen can reduce the elevated pressures and/or pulmonary resistances.[4] Accompanying the improved pulmonary hemodynamics, patients have demonstrated improved exercise capacity.[4]

Oxygen delivery is the fundamental task of the integrated cardiopulmonary system. The adequacy of peripheral oxygen delivery relative to demand can be clinically inferred from the mixed venous oxygen tension ($P\bar{v}O_2$) or saturation.[6] Among patients with COPD, the finding of a low $P\bar{v}O_2$ is a bad prognostic sign.[7] Improved $P\bar{v}O_2$ in response to oxygen therapy is a good prognostic sign.[7]

From the viewpoint of exercise physiology, it has been a uniform observation among patients with COPD, and normal subjects, that with progressive exercise, $P\bar{v}O_2$ declines. At maximal exercise, $P\bar{v}O_2$ reaches similarly low levels in normals and COPD patients.[8] Because arterial content changes little or increases with exercise in COPD patients, the fall in $P\bar{v}O_2$ appears to be primarily a failure of the cardiac output to increase as rapidly as the oxygen demand.[8]

Cardiac output is the most important component of the oxygen delivery chain. With compensatory threefold increases in cardiac output, resting levels of hemoglobin of 5 g % *or* of PaO_2 of 35 mm Hg can be tolerated without decline in resting oxygen delivery. On the other hand, compensatory increases in either hemoglobin or PaO_2 cannot maintain oxygen delivery if cardiac output cannot be maintained. In every disease of the heart and lungs, maintenance of forward cardiac output is critical to survival, and reserve of cardiac output increase is critical to exercise capacity. The suggestion that COPD patients exercise cardiac outputs are "within the normal range" relative to oxygen consumption, is correct *but* normal subjects are also limited by their ability to increase stroke volume *not* by ventilation.[8] Furthermore, because resting arterial oxygen content of COPD patients is mildly reduced, a "normal" cardiac output may be inadequate.[8]

In patients with chronic obstructive pulmonary disease, the primary limitation to "forward" cardiac output is right heart function (including right heart preload or venous return). It is clear that right ventricular dysfunction is common in COPD, and that it is worse during exercise.[9] In the absence of concomitant valvular, ischemic or systemic hypertensive disorders, cardiac output is not limited by left ventricular dysfunction in these patients.

Resting studies of COPD patients have demonstrated an inverse relationship between pulmonary hemodynamics and right ventricular ejection fraction.[10] These relationships are not perfect because the RVEF is but one measure of right ventricular systolic function.[11] The relationship between pulmonary hypertension and right ventricular dysfunction in COPD patients has been strengthened by Marmor and coworkers[12] who used both the RVEF and the right atrial emptying rate, a measure of right ventricular diastolic function, to assess right ventricular function.

Exercise studies by Mahler and coworkers[13] and more recently by Morrison et al[8] have demonstrated the link between pulmonary hypertension and right

ventricular dysfunction among patients with COPD.

Pulmonary hypertension leads to right ventricular systolic and diastolic dysfunction by elevating afterload and reducing right ventricular myocardial oxygen supply relative to demand. Pulmonary hypertension can lead to right ventricular ischemia and dysfunction in the absence of coronary disease (Morrison et al, unpublished). The mechanism by which pulmonary hypertension increases myocardial oxygen demand is by increasing systolic wall stress. Conversely, pulmonary hypertension can be expected to increase coronary resistance and thereby decrease coronary flow. Right ventricular ischemia secondary to pulmonary hypertension has been documented in animal models and the hypothesis has been advanced that pulmonary hypertension is a major determinant of whether the right ventricle will infarct.[14] Among the several reasons to emphasize right ventricular ischemia in the morbidity of COPD patients are that this problem is *not* likely to be ameliorated by vasodilators, especially if these substances only reduce pulmonary resistance. This may be part of the explanation for the disappointing clinical experience with nearly every pulmonary vasodilator except one: low flow oxygen.

Oxygen therapy helps those chronic obstructive pulmonary disease patients who can increase cardiac output. Data from the NOTT study and our own work suggest that oxygen therapy benefits those COPD patients who have an increase in forward stroke volume.[2,15] In the acute setting, Degaute et al[16] have shown that oxygen can actually be associated with decreased oxygen delivery in COPD patients, *if* they have an acute decline in cardiac output. The complex system devised by Mithoefer and coworkers[17] can be simplified: mixed venous oxygen levels can be maintained with or without arterial hypoxemia, *if cardiac output is maintained.* The findings reported by Ashutosh et al in this issue are consistent with studies cited in this editorial. First, exercise Vo_2 is determined by the ability to increase cardiac output; therefore, the patients who could increase cardiac output were selected by the exercise test. Second, response of pulmonary pressure to oxygen was associated with improved survival. Because the changes in resting pulmonary hypertension were small, it is not surprising that the resting RVEF changes (in a subset of patients) were not large enough to discriminate between the two groups.

That pulmonary hypertension is an important determinant of the quality and quantity of life among patients with COPD is no longer in doubt.[18] The question is: "How does pulmonary hypertension lead to the reduced quality and quantity of life?" Based upon the foregoing, we propose *The Right Ventricular Hypothesis: Pulmonary hypertension leads to reduced quantity and quality of life of COPD patients by means of impaired right ventricular systolic and diastolic function.*

Douglass Andrew Morrison, M.D., F.C.C.P.
Denver

Director, Cardiac Catheterization Laboratory, Veterans Administration Medical Center.
Reprint requests: Dr. Morrison, University of Colorado Health Science Center, 4200 East Ninth Avenue, Denver 80262

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Abstracts of Clinical Investigations

A New and Standardized Format

I witnessed an historic innovation in biomedical communications during my tenure as a Senior Editor of the *Journal of the American Medical Association* from 1962 to 1967. During this period, the summary and conclusions of articles were moved to the beginning of each report in JAMA. This move gladdened the hearts of the non-physician science writers who worked closely with us in publicizing scientific investigations published in AMA journals. I recall one distinguished lay-journalist who teased our editorial staff by noting, "I don't understand the philosophy of physician editors! A fundamental precept in journalism is that in the opening paragraphs the author should provide for the reader the key messages which his story is intended to convey. Instead of following this principle, you medical editors keep as a deep dark secret the major conclusions of every study. The summary appears on the last page and the reader may have to plow through hundreds of words of discussion and other details before he can get to the summary! I'm glad you folks have entered the 20th Century!"

JAMA and the *Canadian Medical Journal* were the first to adopt this new role for abstracts, and other journals, including the *Lancet*, the *New England Journal of Medicine* and the *Annals of Internal Medicine*, followed suit soon thereafter. Today it is the rare biomedical publication which does not feature a summary or an abstract at the beginning of each major scientific report. This change was particularly timely because the transition to computer storage and retrieval of scientific data occurred at approximately the same time. The presence of an informative abstract as the introduction to medical reports was of enormous assistance to computerization in institutions such as the National Library of Medicine and other national and international data banks. These national and international computerized services are now available to those who possess personal computers, as well as to medical libraries. Currently, it is possible to obtain abstracts *or* complete articles through computerized services. The recent emphasis on informative abstracts has made the tasks of the investigator, teacher and clinician infinitely more productive.

The worldwide acceptance of the abstract indicates the unique importance of this element of medical journalism. I am indebted to Dr. Edward Rosenow, a member of the Editorial Board of *Chest*, for his suggestion that we consider implementing in our journal a new concept proposed by an ad hoc working group for critical appraisal of the medical literature.[1] This group suggested that "A solution to some of these information problems is for authors of articles with direct clinical implications to prepare their abstracts so that key aspects of purpose, methods and results are consistently described in a standardized manner with a partially controlled vocabulary."[1] The working group prepared an outline of the information which they believe readers most need to discern the validity and applicability of an article "reporting a preplanned clinical investigation." They indicated that the key information needed by clinicians for selecting articles of high relevance and quantity were as follows:

1. *Objective:* the exact question(s) addressed by the article.
2. *Design:* the basic design of the study.
3. *Setting:* the location and level of clinical care.
4. *Patients or Participants:* the manner of selection and numbers of patients or participants who entered and completed the study.
5. *Interventions:* the exact treatment or intervention, if any.
6. *Measurements and Results:* the methods of assessing patients and key results.
7. *Conclusions:* key conclusions including direct clinical applications.

Preparation of abstracts in accordance with these new guidelines means that many would exceed the maximum of 150 words which we identify in "Preparation of Manuscripts." However, the importance of enhancing the value of abstracts for our readers makes it imperative that we offer an experimental period to give the authors the option of preparing longer abstracts (synopses) than currently permitted. We propose that abstracts which are prepared in accordance with these new guidelines may be 250 words for articles less than ten typewritten pages in length, and 300 words for longer articles. There will be no change in the synopses or abstracts for other departments such as case reports, special departments and review articles.

In accordance with the proposals cited above, we have modified the description of the preparation of the synopsis (abstract), page 52. Authors may wish to refer to the more detailed account of the preparation of such a summary which appears in the *Annals of Internal Medicine* 1987; 106:598-604. The Editorial Board of *Chest* and I would appreciate receiving your criticism and comments in the months ahead. We are eager to hear from you.

Alfred Soffer, M.D., F.C.C.P.
Park Ridge, Illinois