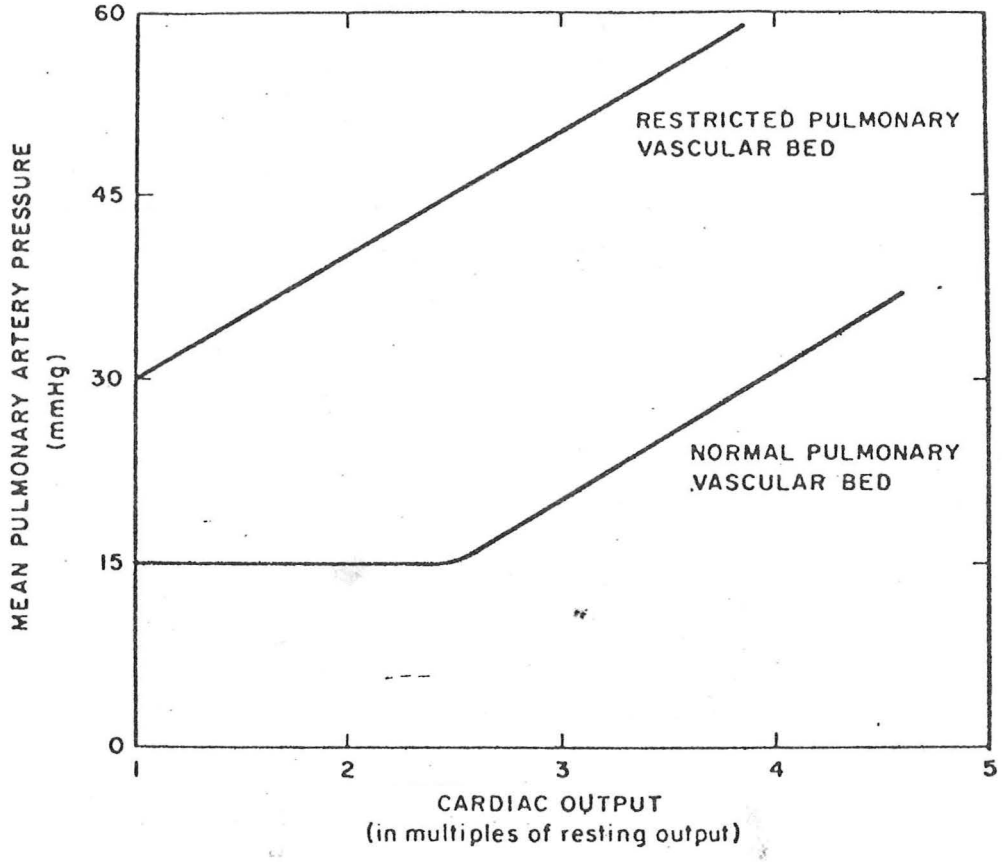
CHRONIC COR PULMONALE



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I. Introduction

The pulmonary circulation plays a pivotal role in the gas exchange function of the lungs, and, therefore, in the ultimate delivery of oxygen to the tissues. The central location of the pulmonary circulation - interposed between the two sides of the heart, coupled with its intimate relationship with the airspaces, render this vascular network vulnerable not only to disorders which may affect it primarily, but to conditions which alter the structure or function of the heart and lungs as well. This discussion will focus on chronic respiratory conditions which affect the pulmonary circulation at a site proximal to the capillaries.

A. Background

Laennec described the clinical and pathological features of emphysema in 1826, and noted that severe lung disease may produce heart failure:

> "All diseases which give rise to severe and long continued dyspnoea produce, almost necessarily, hypertrophy or dilatation of the heart, through the constant efforts the organ is called on to perform, in order to propel the blood into the lungs against the resistance opposed to it by the cause of the dyspnoea . . . When, however, diseases of the heart are found to coexist with chronic pleurisy, phthisis, emphysema, and, in general, with chronic disease of the lungs, it will usually be found, on close examination, that the latter are the primary diseases. It follows from these, and other facts noticed under the head of emphysema and pulmonary catarrh, that a neglected cold is frequently the original cause of the most severe diseases of the heart". (1)

In 1901 Ayerza described a case of sclerosis of the pulmonary arteries in association with profound cyanosis and chronic dyspnea (2). In 1931 Dr. Paul Dudley White coined the term "cor pulmonale" to describe abnormalities of the heart resulting from pulmonary parenchymal or vascular disease (3), thereby bringing this disorder to wider clinical attention.

B. Definition of Cor Pulmonale

In 1960 an expert committee of the World Health Organization convened to address several issues concerning cor pulmonale. The definition of cor pulmonale agreed upon by that committee has been widely accepted and is the most precise:

"Hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lung, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart disease". (4)

The terms "cor pulmonale" and "pulmonary heart disease" can be used synonymously. Although cor pulmonale is frequently equated with right-sided heart failure, it is worth emphasizing that right heart failure is a late manifestation of cor pulmonale and need not be present to entertain that diagnosis (5,6). The earliest and most consistent feature of cor pulmonale is an elevation in pulmonary artery pressure or vascular resistance, measured at rest or during exercise. It is this increased right ventricular afterload which ultimately leads to right ventricular hypertrophy and/or dilatation.

C. Classification

The classification of chronic pulmonary heart disease proposed by the WHO committee is based on causative diseases, and is shown, with minor modifications in Table 1.

Table I. Classification of Cor Pulmonale Based on Causative Diseases

1. Diseases Affecting Air Passages of the Lung and Alveoli
   a. Chronic obstructive pulmonary diseases (ref. 5,12-19)
   b. Cystic fibrosis (ref. 20-23)
   c. Congenital developmental defects (ref. 24)
   d. Infiltrative or granulomatous diseases
      (1) Idiopathic pulmonary fibrosis (ref. 25-28)
      (2) Sarcoidosis (ref. 7,8,29-31)
      (3) Pneumoconiosis (ref. 12,32-34)
      (4) Scleroderma (ref. 35,36)
      (5) Mixed connective tissue disease (ref. 37-39)
      (6) Systemic lupus erythematosus (ref. 40,41)
      (7) Rheumatoid arthritis (ref. 42-45)
      (8) Polymyositis (ref. 9)
      (9) Eosinophilic granuloma (ref. 46,47)
      (10) Malignant infiltration (ref. 48)
      (11) Radiation (ref. 49)
   e. Upper airway obstruction (ref. 50)
   f. Pulmonary resection (ref. 51-53)
   g. High altitude disease (ref. 54-56)
2. Diseases Affecting Thoracic Cage Movement
   a. Kyphoscoliosis (ref. 57,58)
   b. Thoracoplasty (ref. 52)
   c. Pleural fibrosis (ref. 4)
   d. Neuromuscular weakness (ref. 59,60)
   e. Sleep apnea syndromes (ref. 61-64)
   f. Idiopathic hypoventilation (ref. 59,65-67)
3. Diseases Affecting the Pulmonary Vasculature
   a. Primary diseases of the arterial wall
      (1) Primary pulmonary hypertension (ref. 68)
      (2) Granulomatous pulmonary arteritis (ref. 29,43,44,69,70)
      (3) Toxin-induced pulmonary vascular disease
         a) Aminorex fumarate (ref. 71-73)
         b) Intravenous drug abuse (ref. 10,11,74-77)
      (4) Chronic liver disease (ref. 78-85)
      (5) Peripheral pulmonic stenosis (ref. 86)
   b. Thrombotic disorders
      (1) Sickle cell disease (ref. 87,88)
      (2) Pulmonary microthrombi (ref. 89)
   c. Embolic disorders
      (1) Thromboembolism (ref. 90-96)
      (2) Tumor embolism (ref. 97-101)
      (3) Other embolism (Amniotic fluid, air) (ref. 102)
      (4) Schistosomiasis and other parasites (ref. 103,104)
4. Pressure on the Pulmonary Vasculature by Mediastinal Tumors, Aneurysms, Granulomata or Fibrosis (ref. 105-109)

These conditions include primary disorders of the pulmonary vasculature as well as diseases affecting the lung parenchyma or the thoracic cage which interfere with efficient intrapulmonary gas exchange. While this classification is useful because it emphasizes the different pathophysiologic mechanisms responsible for the development of cor pulmonale, it should be kept in mind that considerable overlap in mechanisms may exist in some conditions. For example, while sarcoidosis generally produces cor pulmonale as a result of pulmonary interstitial disease, pulmonary vascular granulomata may also cause or contribute to pulmonary heart disease in this condition (7,8). Primary vascular involvement with polymyositis, without evidence of parenchymal lung disease, has been reported (9). Similarly, intravenous drug abusers may have evidence of interstitial lung disease as well as primary vascular abnormalities (10,11).

D. Incidence

While a variety of conditions may be associated with pulmonary heart disease, patients with chronic obstructive lung disease comprise the largest group in which cor pulmonale occurs, accounting for over 80 percent of cases in the United States and other industrialized countries (108-110). It has been estimated that between 16 and 38 percent of hospital admissions for congestive heart failure in this country are related to exacerbations of cor pulmonale (111). Chronic lung diseases affect approximately 47 million people in this country and account for over 80,000 deaths per year. Equally sobering is the fact that chronic respiratory disease is the most rapidly increasing of the top ten leading causes of death in the U.S., rising at a rate of 1.4 percent per year (112). If one accepts the estimate that cor pulmonale accounts for approximately 10 percent of heart disease in this country (113), then next to hypertensive and atherosclerotic heart disease, cor pulmonale is the most common cardiac condition in patients beyond the fifth decade of life.

The importance of coexistant pulmonary hypertension in the setting of chronic lung disease lies not only with its contribution to the morbidity from lung disease, but also to its impact on survival. Burrows et al (114) reported that the presence and severity of pulmonary hypertension correlated more closely than any other variable with survival in a series of patients with chronic lung disease: In their study, no patient with a pulmonary vascular resistance >550 dynes sec cm^{-5} survived three years, while 36 percent of patients with severe obstructive lung disease (FEV_1 <0.85 litres) without pulmonary hypertension survived three years or longer (Figure 1).

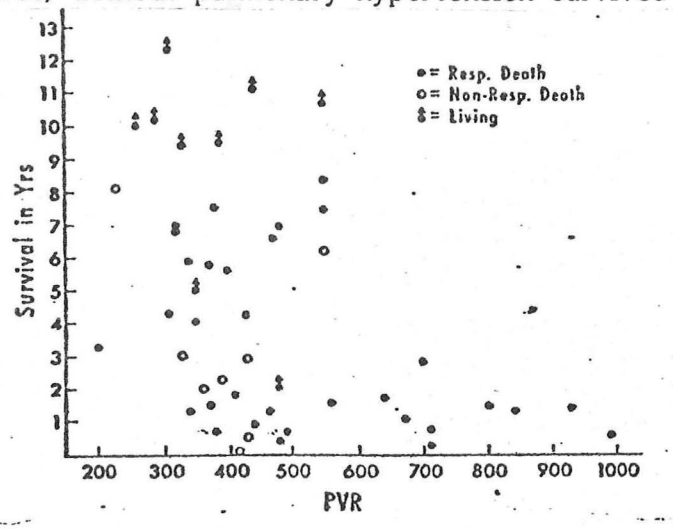

Figure 1. Relation of survival to pulmonary vascular resistance (PVR). From ref. 114.

Similarly, Bishop (115) studied a group of 128 patients with chronic bronchitis: 90 percent of patients with a normal pulmonary arterial pressure at the time of initial evaluation were alive five years later, and mortality rates in patients with elevated pulmonary artery pressure increased progressively with increasing levels of pulmonary artery pressure. Less than 10 percent of Bishop's patients with a mean PA pressure of 45 mmHg or higher were alive at five years (Figure 2).

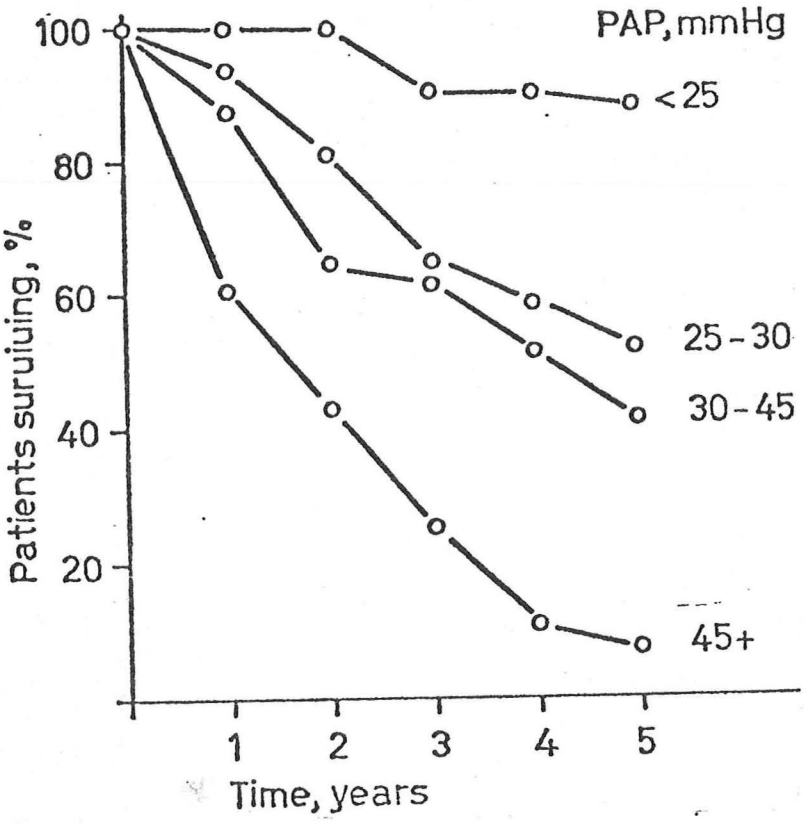

Figure 2. Relationship between survival and the level of mean pulmonary artery pressure (PAP) in patients with COPD. From ref. 115.

Traver et al (116) reported a mortality rate of 50 percent at 13.5 years in patients with high values for post-bronchodilator FEV_1 when there were no signs of cor pulmonale, and a 50 percent mortality rate at 7.0 years in patients with comparable spirometric values in whom signs of cor pulmonale were present (Figure 3).

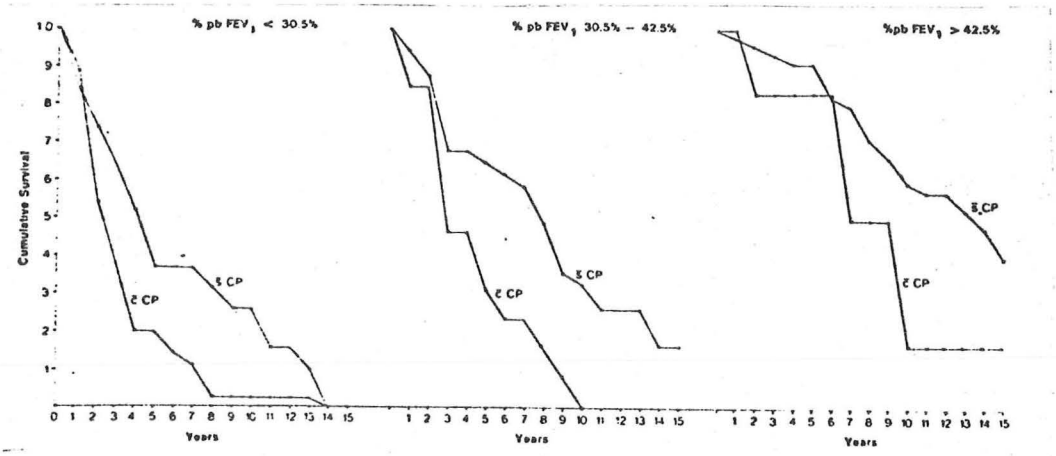

Figure 3. Effect of cor pulmonale (CP) on survival in subjects less than 65 years of age divided into 3 groups according to their percent predicted postbronchodilator forced expiratory volume in 1 sec (% pb FEV_1); $\overline{c}$ = with, and $\overline{s}$ = without.

II. Pathogenesis

The normal pulmonary circulation can accomodate a maximal right ventricular output with an increase in driving pressure of only several millimeters of mercury by one or both of two adaptive mechanisms - distention of existing vessels or recruitment of unused vessels. Patients with chronic lung diseases have larger than normal increases in pulmonary artery pressure with maneuvers which increase blood flow, such as exercise (117-119), even at the stage when resting hemodynamics are normal, implying an inability to either further dilate the vasculature or recruit additional ususued vasculature. Conditions such as emphysema and pulmonary fibrosis destroy large segments of lung parenchyma, but it is unlikely that loss of cross-sectional surface area of the pulmonary vascular bed accounts for all the elevation in perfusion pressure because pulmonary hypertension is, at least in part, reversible in these conditions. Furthermore, experiments using dogs have demonstrated that two-thirds of the lung parenchyma must be ablated before pulmonary artery pressure is appreciably increased (120).

It is generally accepted that the derangements in intrapulmonary gas exchange which occur in chronic lung disease produce the major inciting stimuli for the development of cor pulmonale. Alveolar hypoxia is a potent stimulus for constriction of precapillary pulmonary vessels (121,122), and acidosis or hypercarbia potentiate this effect (123-125) (Figures 4 & 5).

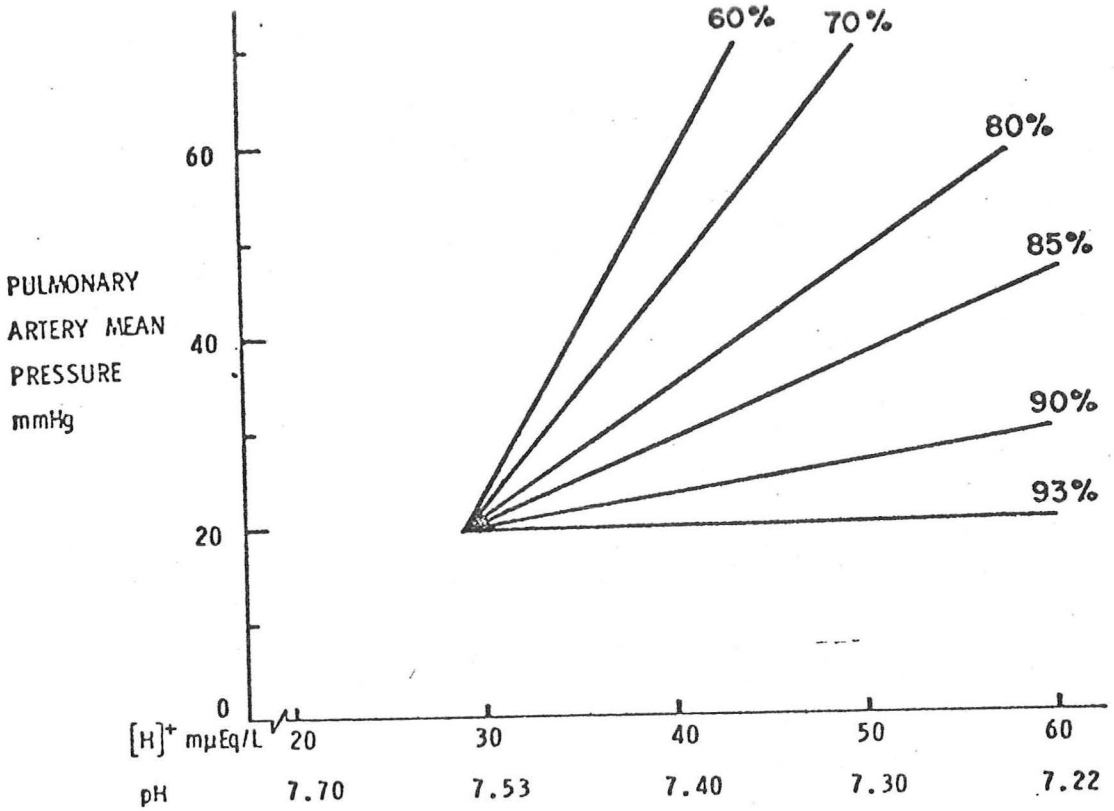

Figure 4. The relation between mean pulmonary artery pressure and arterial oxyhemoglobin saturation and different levels of blood pH or hydrogen ion concentrations. From ref. 124.

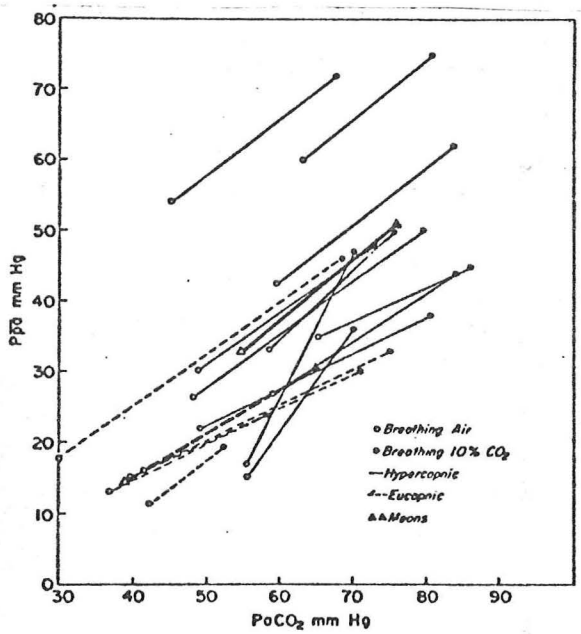

Figure 5. Effect of 10% CO_2 breathing on pulmonary artery pressure at rest in 11 hypercapnic and 5 eucapnic patients.

The pulmonary vasoconstrictor effects of alveolar hypoxia appear to be a locally mediated phenomenon, since an hypoxic pressor response can be elicited in denervated lungs in vivo and in isolated perfused lung systems (126). These observations have prompted a search for chemical mediators which may be responsible for hypoxic pulmonary vasoconstriction (Figure 6).

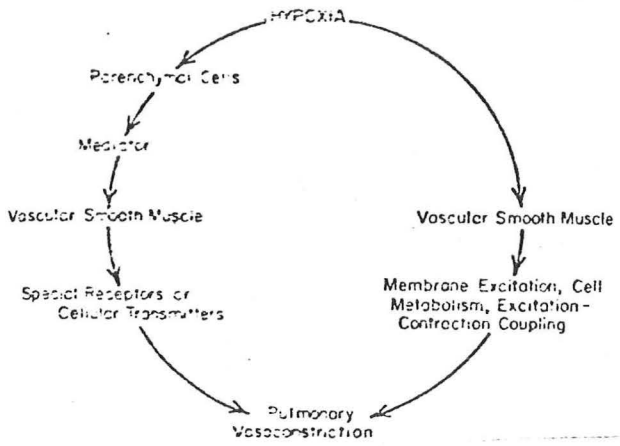

Figure 6. Alternate hypotheses to explain hypoxic pulmonary vasoconstriction. Left: indirect mechanism - mediator released by non-muscle cells of the lung diffuses to vascular smooth muscle, where it engages cellular receptors and mechanisms to activate the contractile process. Right: direct mechanism - the effects of hypoxia are exerted directly on vascular smooth muscle by affecting one or more stages in the contractile process: excitation, contraction, or the coupling of the two.

Although several candidates have been advocated, including histamine, serotonin, and eicosanoids derived from both the cyclo-oxygenase and lipoxygenase pathways, there is to date no conclusive evidence supporting a role for any or all of these vasoactive substances as mediators of hypoxic pulmonary vasoconstriction (127) (Table II).

Factors other than alveolar hypoxia may play a role in the genesis and maintenance of cor pulmonale since the use of continuous supplemental oxygen often has little effect on pulmonary artery pressure in lung disease despite improving alveolar and arterial oxygenation. Harris et al (128) suggested that the increased airways resistance in patients with chronic obstructive lung disease may raise the transmural pulmonary vascular pressure and contribute to an increased pulmonary vascular resistance. Recent experiments in intact animals under conditions of controlled lobar flow have suggested that the degree of mixed venous hypoxemia may be an additional stimulus for precapillary pulmonary vasoconstriction (129-131), either by a direct effect or by influencing alveolar PO_2. Secondary

Table II. Pharmacologic Characteristics of Possible Humoral Mediators of Hypoxic Pulmonary Vasoconstriction

Agent	Pulmonary Vasoconstrictor	Lung Storage	Activated Released In Lung	Hypoxic α or β Response	↓ Hypoxic Response by Inhibitor	↓ Hypoxic Response By Depletion
Histamine	++/±	++	++	+	±	+
Serotonin	++	+	+	-	?	
Norepinephrine	++	++	++	+	+	-
Angiotensin II	++	-	++	-	-	±
$PGF_{2\alpha}$	+	-	++	-	-	-
Vasopressin	±	-	-	?	?	?
Bradykinin	±	-	-	?	?	?
Acetylcholine	±	+	+	-	-	-
Leukotrienes	++	-	++	?	+	?

polycythemia may also contribute to the development of pulmonary hypertension in the setting of chronic hypoxia, presumably by increasing blood viscosity and raising both basal vascular resistance and the increase in resistance produced by hypoxia (132). It is also possible that other influences, such as extrapulmonary reflexes stimulated by systemic arterial hypoxemia or other, and as yet undefined, stimuli unique to chronic lung disease may contribute to pulmonary vasoconstriction as well.

The sustained elevation in pulmonary vascular tone which results from active pulmonary vasoconstriction leads to an inexorable sequence of events (Figure 7):

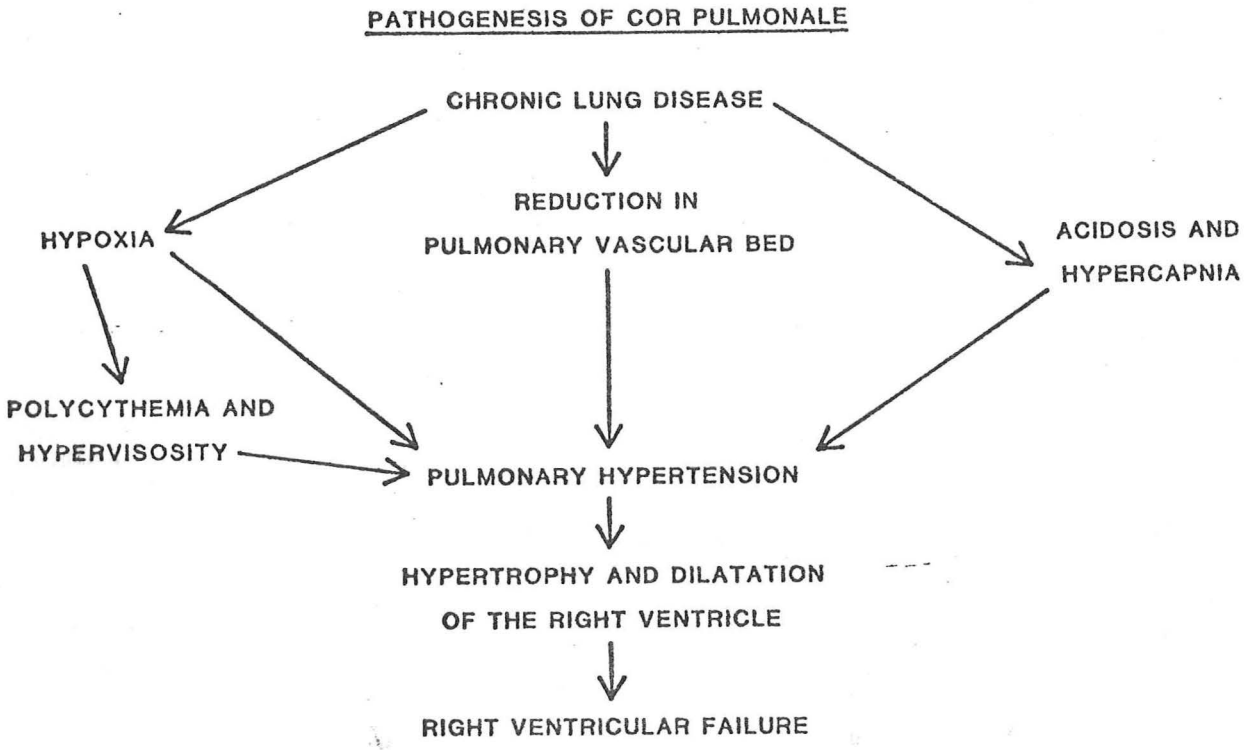

Figure 7. Schema of the pathogenesis of cor pulmonale.

The increased right ventricular afterload causes pulmonary blood flow to decrease and eventually produces overt right heart failure. The decrease in systemic oxygen transport which results from the low cardiac output will produce tissue and mixed venous hypoxemia which, as mentioned previously, may produce a further stimulus for pulmonary vasoconstriction.

The increased work of breathing common to many forms of chronic lung disease (133), coupled with a diminishing oxygen delivery to the respiratory muscles,

can precipitate or contribute further to respiratory failure, hypoxemia and hypercapnia, and therefore produce an additional stimulus for pulmonary vasoconstriction. Additionally, repeated episodes of severe hypoxemia, which may occur during sleep in patients with chronic obstructive lung disease (134) or during episodes of acute respiratory failure may further contribute to the development of a chronic pulmonary hypertensive state - even if these episodes are interposed with prolonged periods of relative normoxia.

III. Left Ventricular Function in Chronic Cor Pulmonale

Left ventricular dysfunction can contribute to the pulmonary artery hypertension in chronic lung disease, primarily by increasing pulmonary venous pressure and secondarily raising precapillary pressure. There has been considerable debate concerning the effects of chronic lung disease on ventricular function, and controversy exists as to the potential mechanisms responsible for left ventricular dysfunction in this setting.

Autopsy studies showing evidence of left ventricular hypertrophy in 10-90% of patients with chronic bronchitis (135-137) provided the earliest suggestion that the left ventricle may be affected by lung disease (Table III). Unfortunately, little clinical data concerning concomitant systemic conditions was provided in most of these reports, and the pathologic criteria used for left ventricular hypertrophy were not uniform. Baum et al (138) reported 15 patients with chronic obstructive lung disease who underwent complete hemodynamic studies; ten of his 15 patients also underwent coronary angiography. Fourteen patients has abnormal left ventricular function curves, and seven had elevations in left ventricular end-diastolic pressure. Only two patients had significant coronary artery disease. The authors concluded that left ventricular dysfunction may be common in patients with chronic lung disease, even in the absence of coronary artery disease or systemic hypertension.

Several potential mechanisms for left ventricular hypertrophy or left ventricular dysfunction have been proposed, although conclusive evidence for any of these hypotheses is lacking:

1. Severe systemic hypoxemia could decrease myocardial oxygen delivery and lead to left ventricular dysfunction. However, while hypoxemia is common in severe, stable lung disease, compensatory polycythemia frequently develops and maintains systemic oxygen transport at near normal levels. It is likely, however, that the LV dysfunction which occurs in patients with decompensated chronic lung disease and acute respiratory failure may be related to an acute deterioration in myocardial oxygen delivery (Figure 8).

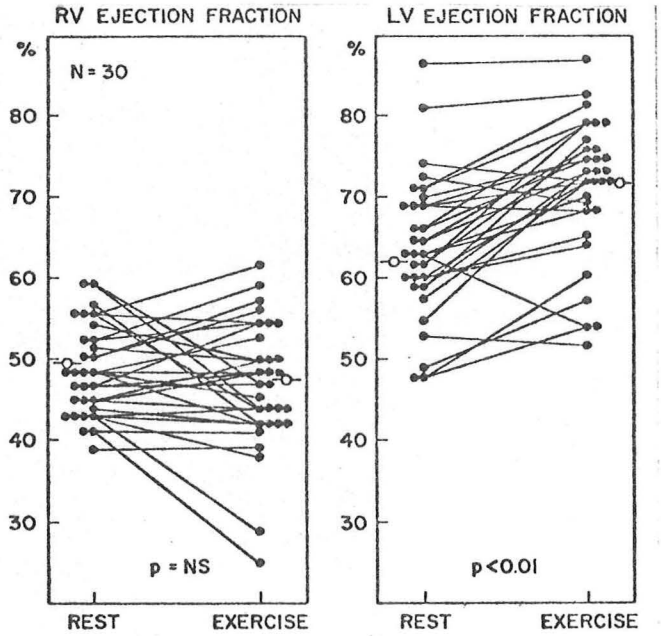

Figure 8. Right ventricular (RV) and left ventricular (LV) ejection fraction at rest and submaximal exercise in 30 patients with COPD.

Table III. The Association of Gross Left Ventricular Changes with Right Ventricular Changes in Chronic Lung Disease with Cor Pulmonale

		RVH/LV		RV/LV		RVH/LVH		RV/LVH	
Author	Total # patients	# of patients	% of total	# of patients	% of total	# of patients	% of total	# of patients	% of total
Brigon (Am Rev Respir Dis 1969; 99:669-695)	40	16	(40)	6	(15)	16	(40)	2	(5)
Ishikawa (Am Rev Respir Dis 1972; 105:358-367)	55	26	(47)	18	(33)	10	(18)	1	(2)
Millard (Br Heart J 1967; 29:43-50)	46	23	(50)	16	(35)	7	(15)	0	(0)

RV = Right ventricular weight <75 gram

RVH = Right ventricular hypertrophy, weight ≥75 gram

LV = Left ventricular weight <190 gram

LVH = Left ventricular hypertrophy, weight ≥190 gram

2. A high cardiac output, occasionally seen in the "blue bloater" with carbon dioxide retention, or left-to-right shunting through broncho-pulmonary anastamoses (139,140), could produce a high-output cardiac failure. The cardiac output in stable chronic pulmonary disease is usually normal (141), and anastamoses, although present pathologically, do not appear to produce a significant left-to-right shunt. Additionally, increased flows, when seen, are usually modest and would not seem adequate of themselves to produce ventricular failure.

3. Abnormal geometry of the left ventricle could impede LV ejection. This hypothesis is based on echocardiographic and angiographic data which show that right ventricular pressure overload causes the interventricular septum to move paradoxically and left ventricular filling and ejection may be limited by an alteration of the spatial geometry of the chamber (138,142,143). Thus, LV performance may be compromised by a distorted configuration of the left ventricle rather than an intrinsic abnormality of the myocardium. In addition, the right ventricular muscle fibers are a syncitium which interlock with the left ventricular fibres. Each RV contraction exerts some tension on the LV. A hypertrophied, hypertensive right ventricle could thereby induce some hypertrophy of the left ventricle.

4. Left ventricular dysfunction or hypertrophy could be secondary to other disease processes and thus merely coincidental. The bulk of reports in which careful selection of stable patients with lung disease were studied support this concept. Frank et al (144) found that left ventricles of 11 patients with chronic cor pulmonale were normal with regard to contractile state, preload, afterload and coronary blood flow. Davies and Overy (145) and Khaja and Parker (146) found no evidence of LV dysfunction in studies of carefully selected, stable patients with chronic lung disease and cor pulmonale. Similarly, Steele et al (147), using radionuclide techniques, found that abnormalities in LV ejection fraction in patients with chronic lung disease could be explained on the basis of coexistant coronary artery disease (Figure 9).

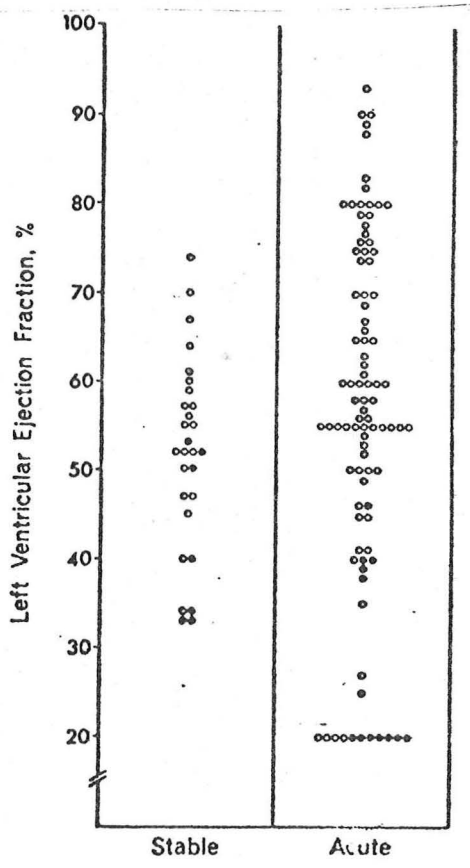

Figure 9. Left ventricular ejection fraction at rest in 28 patients with stable COPD and in 92 patients with acutely decompensated cor pulmonale. Patients with definite concomitant left-sided heart disease are shown in closed circles, patients with no evidence of left-sided heart disease are shown in open circles. From ref. 147.

Murphy et al (148) found left ventricular hypertrophy in 20 of 72 patients (28%) with chronic bronchitis or emphysema: Ten had hypertensive and/or atherosclerotic heart disease, and two had aortic valve disease. Of the remaining 8 patients with left ventricular hypertrophy, the authors speculated that systemic hypertension may have been present but beyond the stringent criteria used for their study. It is thus likely that the presence of left ventricular hypertrophy or dysfunction results not from cor pulmonale per se, but from coexistant cardiovascular disease. Although the spatial orientation of the left ventricle may be distorted in patients with cor pulmonale, it is unclear at this point whether this produces significant hemodynamic abnormalities in most cases (Table IV).

IV. Noninvasive Evaluation

A. The Electrocardiogram

Although several different criteria have been suggested for the ECG diagnosis of right ventricular hypertrophy, the electrocardiogram is not a sensitive tool for the diagnosis of cor pulmonale: Phillips (149) reported that only 30% of 18 cases with autopsy-proven cor pulmonale had ECG evidence of right ventricular hypertrophy, and Kilcoyne (150) found 28 percent of 81 living patients with cor pulmonale had right ventricular hypertrophy by ECG criteria. Ferrer has suggested that the conventional ECG criteria for cor pulmonale are insensitive because they are based on the presence of right ventricular hypertrophy, which is a late manifestation of the disease (151) (Table V).

B. Vectorcardiogram

Wilson et al (152) evaluated 32 patients with chronic obstructive pulmonary disease using cardiac catheterization and the vectorcardiogram. No patient met ECG criteria for right ventricular hypertrophy, but there was a linear correlation between terminal rightward QRS forces and mean pulmonary artery pressure during exercise in patients with posteriorly oriented horizontal loops on VCG. Of 20 patients with hemodynamic abnormalities either at rest or during exercise, 85% had rightward terminal QRS forces of >5 percent of the total loop area measured with a plastic grid. They concluded that the VCG may be more useful than the ECG in identifying early hemodynamic abnormalities in the pulmonary circulation.

C. Echocardiogram

Nanda et al (153) in 1974 suggested that the echocardiogram of the pulmonary valve was useful in evaluating the severity of pulmonary hypertension. His patient population, however, consisted of patients with post-capillary pulmonary hypertension and was devoid of cases of cor pulmonale. Acquatella and associates (154) studied 29 patients with congestive heart failure (none with cor pulmonale) and was able to adequately visualize the pulmonic valve in sixteen. He found no correlation between hemodynamic measurements and any single abnormality of the pulmonic valve. Recently, Boyd et al (155) studied 17 patients with chronic lung disease and found a close relationship between the pulmonary artery diastolic pressure and the time interval between tricuspid valve closure and pulmonary valve opening.

The major limitation to the usefulness of echocardiography in cor pulmonale, however, has been that hyperinflation of the lungs often precludes adequate visualization of the cardiac chambers and valves, and may be accomplished in only 60 percent of patients with chronic obstructive pulmonary disease (155). Nevertheless, if an adequate study can be performed, echocardiography may be useful not only in suggesting the presence of pulmonary hypertension but also in monitoring the effects of therapy (Figure 10).

Table IV. Catheterization Data at Rest in Patients with COPD and Cor Pulmonale

Author	Total Number of Patients	Number of Patients with PCWP or LVEDP* >16 mmHg at rest
Jezek	19	4
Rubin	38	5
Christianson	19	-
Kline	20	2
Lourides	13	1
Rice	7	1
Krayenbuehl	10	2
Dexter	15	-
Herles	92	12
Rao	4	3
Segel	15	3
Lockhart	86	12
Matthay	9	-
Baum	15	4
Parker	9	-
Parker	10	1
Davies	12	-
Jezek	32	1
Evans	47	3
Williams	16	-
Khaja	20	-
Moret	22	1
Horsfield	17	3
Weitzenblum	32	-
Stern	29	5
TOTAL	608	62

Percent abnormal PCWP and/or LVEDP 62/608 = 10%

* LVEDP, left ventricular end diastolic pressure

PCWP, pulmonary capillary wedge pressure

Table V. ECG Signs of Right Ventricular Hypertrophy

I. Early changes signaling right ventricular abnormality
   1. Shift of QRS axis >30° to the right
   2. Inverted, biphasic or flattened T waves in V_1-V_3
   3. ST segment depression in II, III, and avF
   4. Right bundle branch block

II. Right ventricular hypertrophy
   1. Dominant R wave in avR, V_1, or V_4R
   2. Dominant S wave in V_5 and V_6
   3. Frontal plane axis >+90°
   4. p wave $\geq$2.5 mm

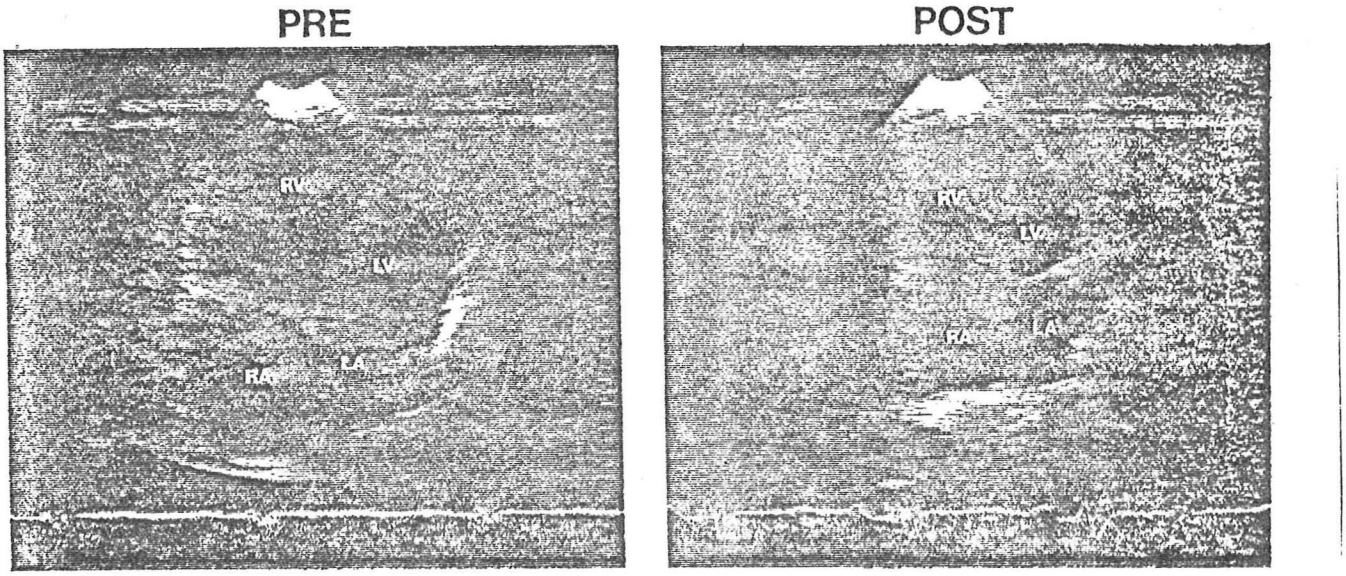

Figure 10. Two dimensional echocardiogram of a patient with pulmonary fibrosis and cor pulmonale before and after institution of therapy. Note the diminution in size of the right atrium (RA) and right ventricle (RV).

D. Radionuclide Angiocardiography

Radionuclide angiocardiographic techniques have been used to evaluate both right and left ventricular function in patients with pulmonary disease. Berger et al (156) compared right ventricular function in patients with chronic obstructive pulmonary disease with normal subjects and found a wide variability in RV ejection fraction in patients with chronic obstructive pulmonary disease (COPD), with a range of 19 to 71 percent (Figure 11). All 19 patients with right-sided heart failure, however, had a reduced RV ejection fraction. Although it is often difficult to isolate and adequately quantify RV function in patients with dilated right ventricles, radionuclide techniques provide a promising tool for noninvasive evaluation of RV function in cor pulmonale, and may be particularly useful in monitoring the effects of therapy (vide infra).

E. Pulmonary Function Testing

Abnormalities in pulmonary function may suggest the likelihood that coexistant pulmonary hypertension is present in the setting of lung disease, and may provide an indication of its magnitude. Enson (157) evaluated over 30 patients with interstitial lung disease and reported that, when the vital capacity is between 50-80 percent of predicted the pulmonary vascular resistance is increased, but pulmonary artery pressure is increased only during exercise. When vital capacity is <50 percent, pulmonary artery hypertension is usually present even at rest (Figure 12). Similarly, Timsit and his colleagues (158) and others have found a relation between vital capacity or FEV_1 and the presence of pulmonary hypertension in obstructive lung disease (Figure 13). Ferrer and others have demonstrated an inverse relationship between pulmonary artery pressure and arterial hemoglobin saturation (159) (Figure 14).

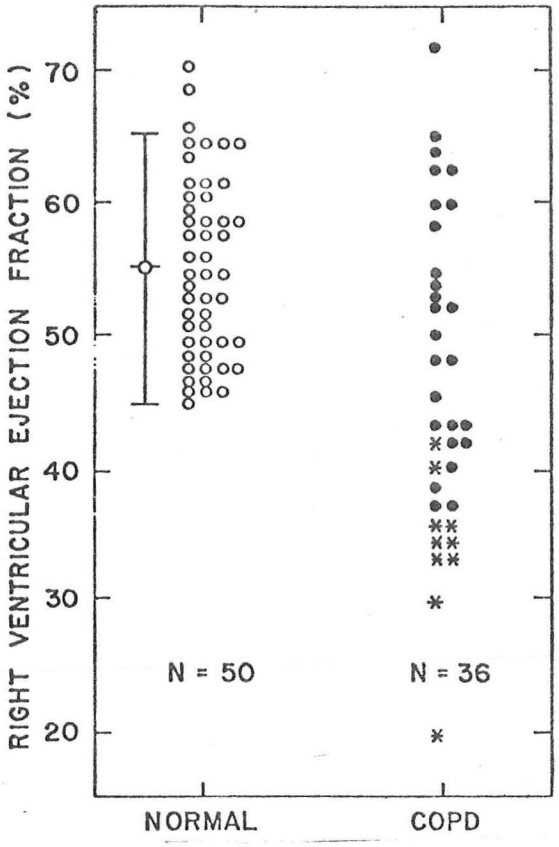

Figure 11. Right ventricular ejection fraction in 50 normals and 36 COPD patients. The lower limit of normal is 45 percent. All 10 patients with a history of decompensated cor pulmonale (denoted by *) had abnormal RV ejection fraction. From ref. 156.

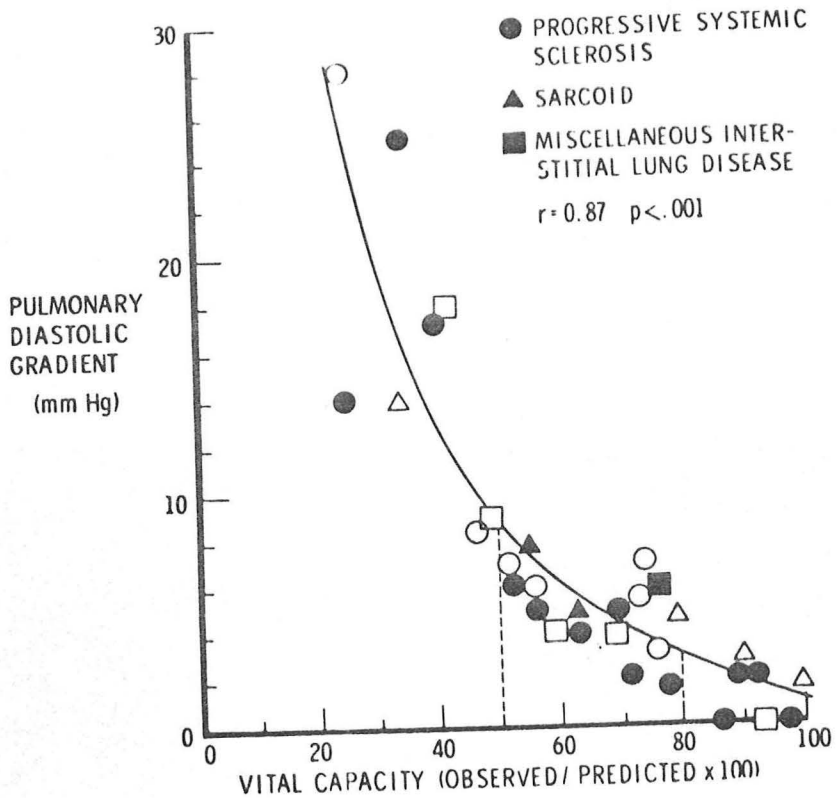

Figure 12. The relationship between the pulmonary diastolic gradient (PAd-PCW) and the percent of predicted vital capacity in patients with interstitial lung disease. From ref. 157.

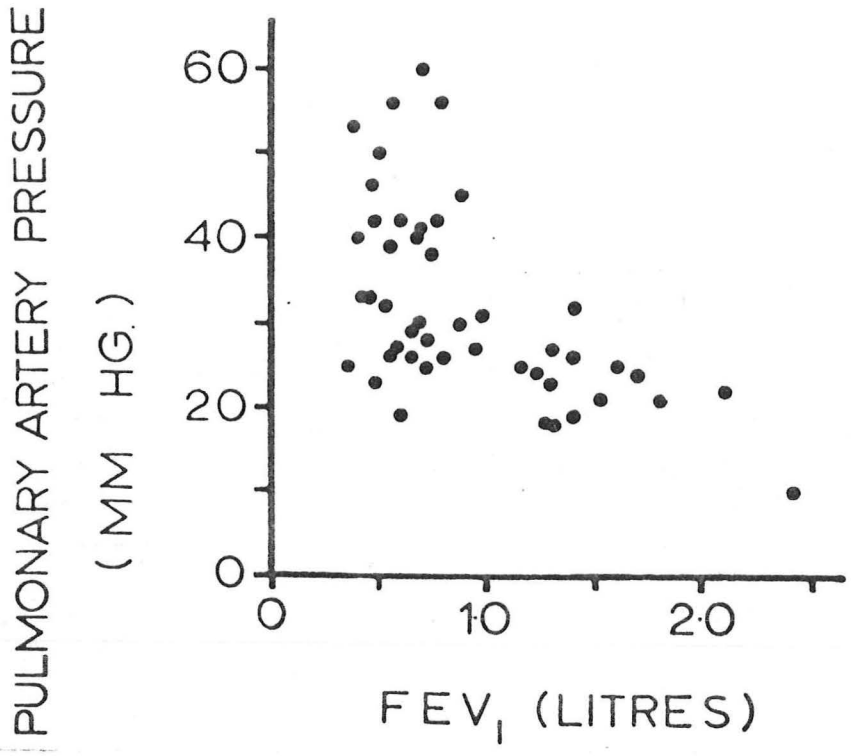

Figure 13. The relationship between the forced expiratory volume in one second (FEV_1) and mean pulmonary artery pressure in 47 patients with severe, stable COPD.

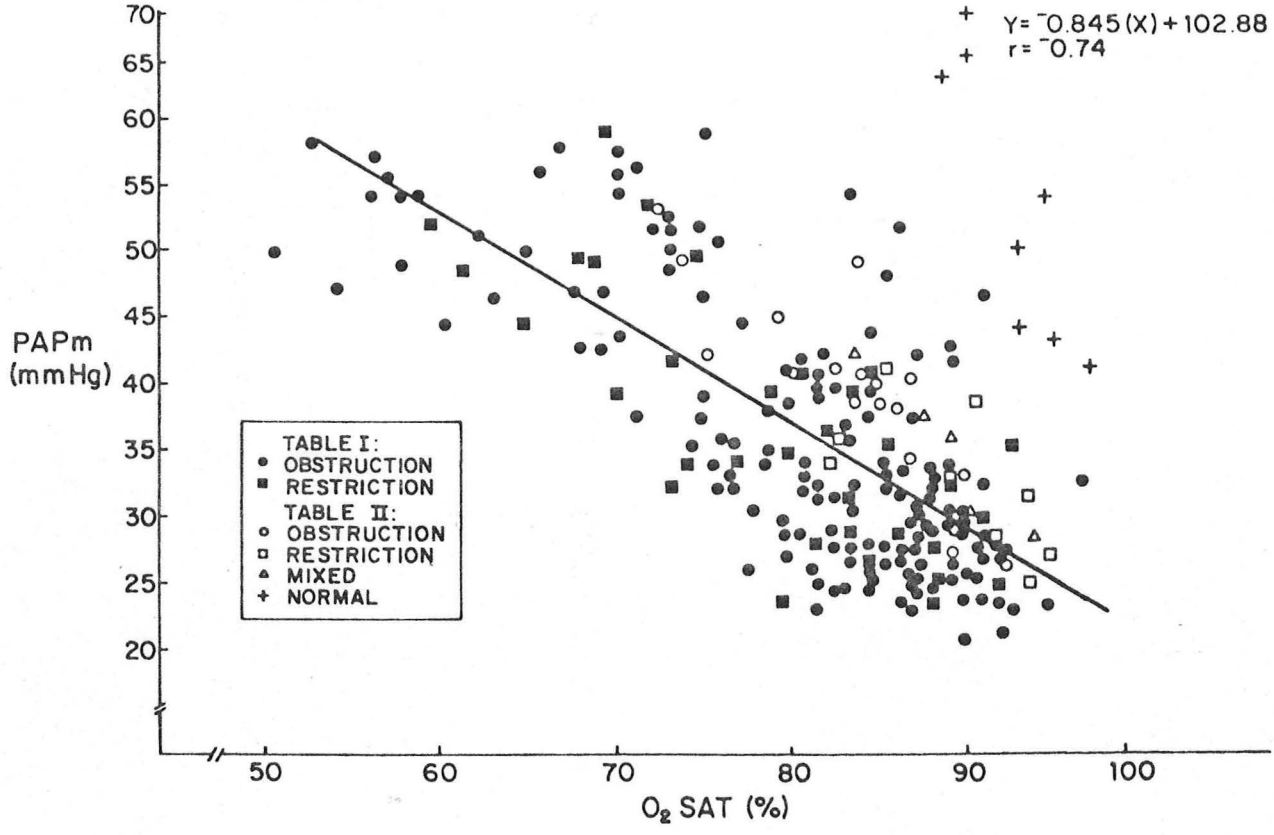

Figure 14. The relationship between the arterial oxygen saturation (O_2 sat) and mean pulmonary artery pressure (PAPm) in 183 patients culled from the literature (closed symbols) and 41 patients studied at this institution (open symbols).

V. Therapy

A. General Approach

The primary objective of therapy for cor pulmonale is to treat the underlying disease. Thus, the signs of cor pulmonale resulting from COPD often improve with measures directed at improving airflow, such as bronchodilators, mucolytics, chest physiotherapy and antibiotics. Theophylline compounds may improve hemodynamics in cor pulmonale secondary to COPD in several ways: 1) They may improve airflow and thereby provide more efficient alveolar gas exchange, 2) They may reduce pulmonary transmural vascular resistance by producing bronchodilatation and decreasing intrathoracic pressure, and 3) They may have a modest direct pulmonary vasodilating effect (160,161).

B. Phelbotomy

As a result of chronic hypoxemia, polycythemia frequently develops in order to maintain systemic oxygen transport. Hyperviscosity resulting from polycythemia, however, can further increase pulmonary vascular resistance and exacerbate or contribute to cor pulmonale. Weisse et al (162) evaluated the hemodynamic effects of phlebotomy in 12 patients with cor pulmonale who had hematocrit levels above 55 percent. They found that reducing the hematocrit from a mean of 61 to 50 percent produced significant decreases in pulmonary artery pressure and vascular resistance, accompanied by improvement in exercise performance. No further benefit was obtained by reducing the hematocrit to a mean of 44 percent. Their study suggests that phlebotomy may be a useful therapeutic maneuver when severe polycythemia is present. Recent reports by Chetty et al (163) and Erickson et al (164) provided additional evidence confirming previous observations concerning the beneficial effects of isovolumic phlebotomy.

C. Supplemental Oxygen

The goal of supplemental oxygen therapy is two-fold: To improve symptoms related to impaired tissue oxygen delivery, and to improve pulmonary hemodynamics. Although scattered reports demonstrated individual hemodynamic responses to supplemental O_2 administered under a variety of clinical circumstances (Figure 15), two recent multicenter, controlled, prospective studies have clarified the long-term effects of O_2 therapy (Figure 16).

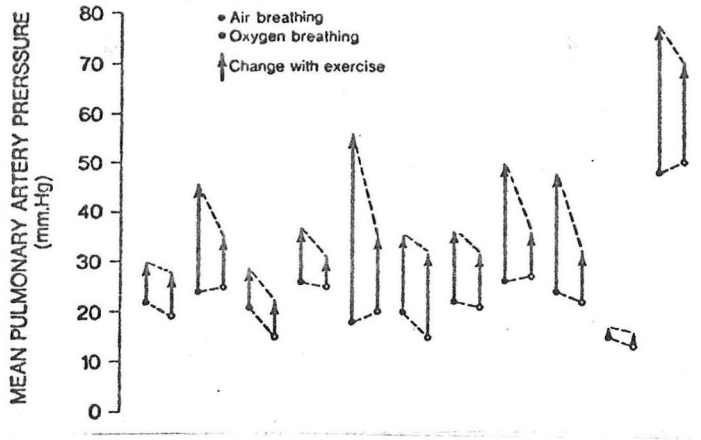

Figure 15. Effects of exercise on mean pulmonary artery pressure in 11 COPD patients with and without O_2. Effects of O_2 may be seen by comparing values connected by dashed lines.

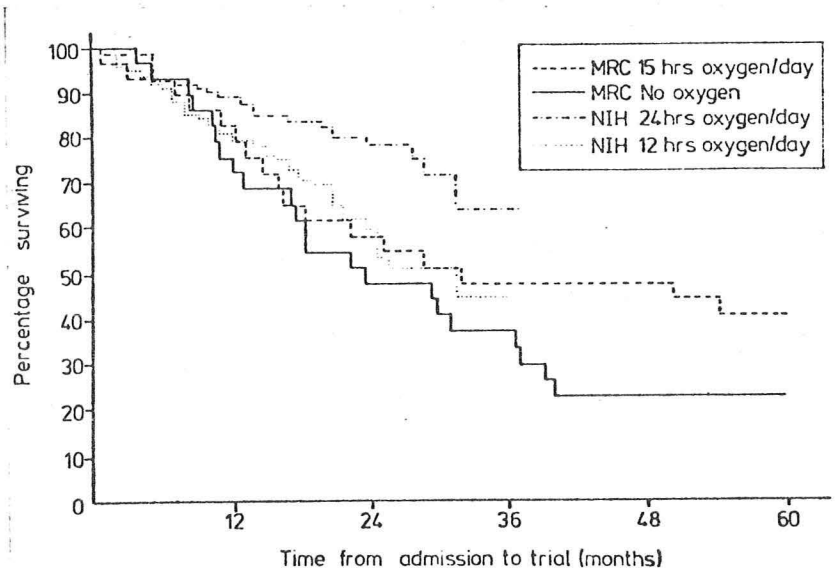

Figure 16. Survival curves in two trials of long-term oxygen therapy (British MRC and American NIH).

The British Medical Research Council study (165) demonstrated that patients with advanced chronic bronchitis who were treated with supplemental O_2 survived longer than patients who did not receive oxygen. Exercise tolerance and quality of life were not critically examined in this study. The Nocturnal Oxygen Therapy Trial (NOTT) (166), a cooperative study performed in the United States, compared physiologic, psychologic and mortality parameters in two groups of patients - those receiving continuous O_2 therapy and those given only 12 hour nocturnal O_2 therapy. Mortality was nearly twice as high in the group receiving nocturnal O_2 alone. Although continuous O_2 therapy reduced pulmonary vascular resistance by 11 percent, the most striking beneficial effects on survival were seen in patients with small decreases in pulmonary vascular resistance, suggesting that the improved survival could not be directly attributed to the improved pulmonary hemodynamics.

The criteria used by the NOTT Study for inclusion are probably the most useful upon which to base the decision of which patients should receive supplemental O_2: a) hypoxemia, i.e. $PaO_2 \leq 55$ mmHg, b) edema, c) hematocrit ≥ 55 percent, and d) P pulmonale on ECG. Ashutosh et al (167) recently suggested adding an additional criteria: Hemodynamic response to supplemental O_2 (Figure 17), since responders had a longer survival than non-responders.

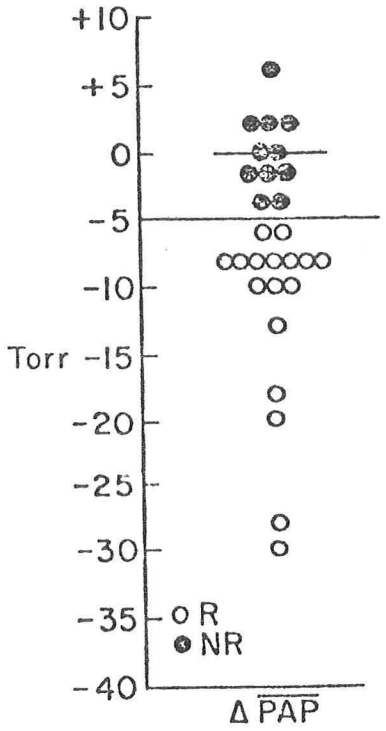

Figure 17. Changes in mean pulmonary artery pressure (ΔPAP) after O_2 breathing for 24 hours in individual subjects. The PAP falls more than 5 mmHg in the responders (R). From ref. 167.

The inspired concentration of O_2 and flow rate should be titrated to the level which produces an arterial PO_2 of 60 torr or greater without producing excessive carbon dioxide retention. Oxygen should be used for >16 hours per day, if possible, and most of this use should be at night, since nocturnal hypoxemia is common in COPD (168,169) and may produce arrhythmias, sudden death or contribute significantly to the development or maintenance of a pulmonary hypertensive state. The pulmonary vascular response to supplemental O_2 is often sluggish and may take weeks or months to achieve its maximal vasodilatation (170). Frequently, oxygen has little effect on pulmonary vascular tone, and the pulmonary vascular responsiveness to oxygen may diminish with time (171). Nevertheless, it may be worthwhile to continue supplemental oxygen therapy in such patients for its other important beneficial effects (166,170).

D. Cardiac Glycosides

The role of cardiac glycosides in therapy for cor pulmonale has been controversial for many years (172). Ferrer showed a reduction in right ventricular end-diastolic pressure after acute digitalization in a group of patients with cor pulmonale (173), and a reduction in right ventricular and pulmonary artery pressure at restudy after several weeks of chronic digitalis combined with intensive pulmonary toilet. In patients with cor pulmonale and normal right ventricular diastolic pressure and stable airways disease, however, Ferrer and others (174,175) have shown that digitalis produces no hemodynamic changes. A recent study by Mathur and his colleagues (176) using radionuclide techniques to quantitate right and left ventricular function demonstrated that digoxin improved RV function only when concomitant LV dysfunction was present (Figure 18).

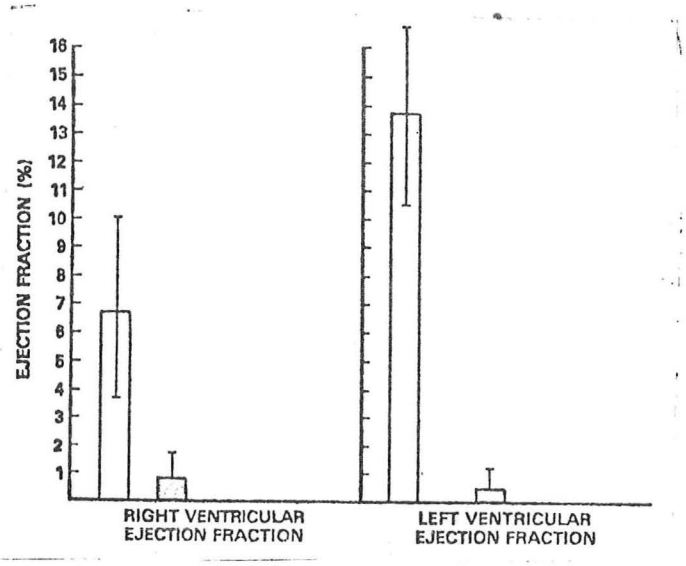

Figure 18. Digoxin increased RV ejection fraction in the 4 patients (open box) whose LV ejection fraction improved, but not in the 11 patients (shaded box) whose LV ejection fraction did not change. From ref. 176.

Additionally, several studies have demonstrated a high incidence of digitalis toxicity in patients with lung disease (172). Thus, the risks of using cardiac glycosides, which are potentiated in cor pulmonale by hypoxemia, hypokalemia if diuretics are used concomitantly, and impaired drug elimination if renal function is abnormal, probably outweigh the potential benefits in most patients without LV failure. Digoxin may be useful in the management of supraventricular arrhythmias, which are common in patients with lung disease, but they should be used only when reversible causes of these arrhythmias, such as hypoxemia, sympathomimetic or other bronchodilator-induced cardiac irritability or metabolic derangements have been excluded.

E. Diuretics

Diuretics have been advocated in the management of cor pulmonale both because they can reduce salt and water retention and because they may have independent effects on alveolar ventilation and pulmonary vascular tone (177-179). Potent diuretics, such as furosemide, can cause hypokalemia and, by by enhancing the reabsorbtion of bicarbonate in the kidney, produce a metabolic alkalosis which is poorly tolerated by the COPD patient with chronic hypercapnia (179-181). In addition, a decreased intravascular volume as the result of aggressive diuresis can reduce right ventricular (179) preload and further decrease cardiac output. It should also be emphasized that edema in the setting of COPD does not necessarily imply the presence of RV failure: Campbell (182) found that the presence of edema correlated more closely with the degree of hypercarbia than with the right atrial pressure. He hypothesized that hypercarbia promoted the reabsorbtion of sodium and water from the kidneys, resulting in an expanded intravascular volume. Additionally, the increased intrathoracic pressures which are common in severe COPD can impede venous return, producing an engorged venous capacitance circuit with an increased peripheral venous pressure.

F. Vasodilators

The concept of vasodilator therapy for left ventricular failure has recently been applied to conditions which exclusively affect the right side of the heart and

the pulmonary circulation (183,184). The rationale for this approach for cor pulmonale is based on the demonstration that right ventricular dysfunction is the result of an increased right ventricular afterload, and that active vasoconstriction constitutes a significant component of the elevation in vascular resistance. A vasodilator which reduces pulmonary vasomotor tone would produce a reduction in right ventricular afterload and an increase in cardiac output (Figure 19).

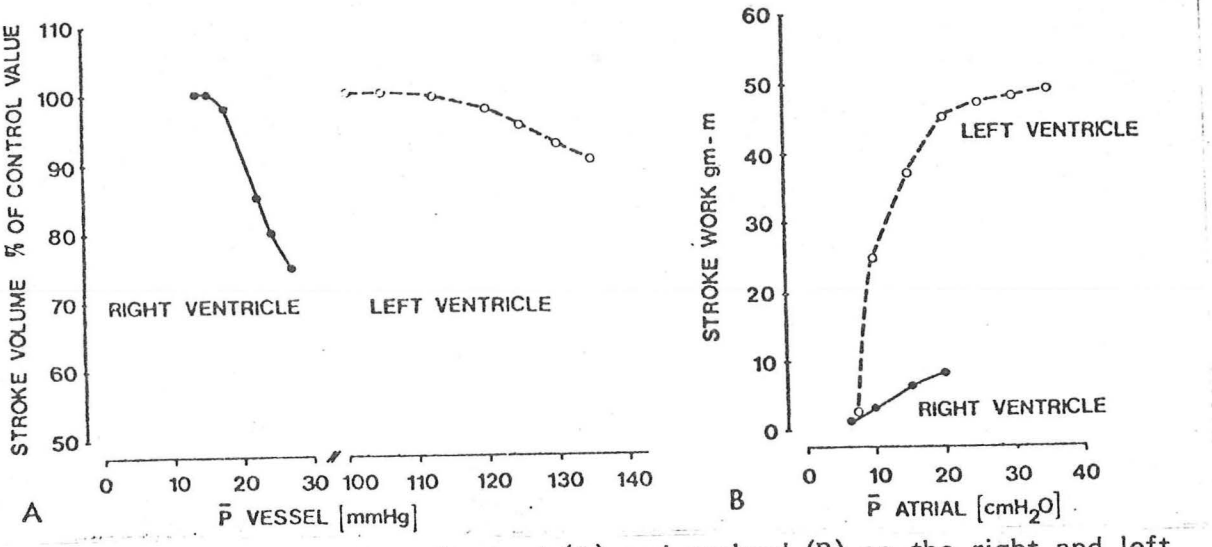

Figure 19. Effects of increasing afterload (A) and preload (B) on the right and left ventricles.

Systemic vascular resistance is reduced as well by vasodilators, but if flow is substantially increased, blood pressure may fall slightly or remain unchanged. Although no specific or even preferential pulmonary vasodilators are available, several potent systemic vasodilators have been reported to exert beneficial hemodynamic effects in the setting of cor pulmonale.

Williams et al (185) and Lockhart et al (186) both demonstrated an increase in cardiac output and a reduction in pulmonary vascular resistance in response to intravenous isoproterenol in patients with COPD and pulmonary hypertension. It is unclear whether the improved hemodynamic state was the result of a direct vasodilatory effect of isoproterenol, or whether an increase in airflow from the known bronchodilator effects of the drug improved gas exchange and indirectly led to a reduction in pulmonary tone.

Phentolamine, an alpha-adrenergic antagonist which has been used to treat patients with persistent fetal circulation and pulmonary hypertension resulting from intracardiac shunts, has also been reported to produce reductions in pulmonary artery pressure and vascular resistance in patients with cor pulmonale, without affecting ventilatory parameters or airflow rates (187,188).

We recently described the acute hemodynamic effects of oral hydralazine in 12 patients with cor pulmonale resulting from obstructive or restrictive ventilatory defects (189). All of the patients had persistent pulmonary hypertension despite being treated with a conventional medical regimen for at least six months. After

48 hours of therapy with hydralazine 50 mg orally every 6 hours, there were significant decreases in mean pulmonary artery pressure and pulmonary vascular resistance and increases in cardiac output, both at rest and during submaximal exercise (Figure 20). Systemic oxygen delivery was increased by 50% (190). We have also demonstrated a reduction in right ventricular end-diastolic pressure in patients with RV failure treated with hydralazine, suggesting that RV function improves with afterload reduction therapy (191) (Figures 21 & 22). Brent and his associates (192) have confirmed these observations (Figure 23), and have demonstrated improved RV function by radionuclide angiocardiography after hydralazine in a series of patients with cor pulmonale (Figure 24). Chappell et al have recently shown that the acute hemodynamic effects of hydralazine in cor pulmonale persisted with chronic therapy (193). The recent demonstration by Simonneau and his associates (194) that nifedipine inhibited hypoxic pulmonary vasoconstriction in 13 patients with acute respiratory failure suggests that this drug may also be useful in the management of chronic cor pulmonale.

The two major potential adverse effects of vasodilator administration to patients with cor pulmonale are systemic hypotension and worsening hypoxemia. The risk of systemic hypotension can be minimized if the intravascular volume is replete and small doses of a vasodilator are used initially. Since not all patients have a beneficial response to vasodilators, **hemodynamic monitoring during the initiation of vasodilator therapy is mandatory.**

Vasodilators can produce or worsen hypoxemia either by increasing perfusion to poorly ventilated lung units (195,196), by recruitment of shunt vessels, or by increasing right-to-left shunting through a patent foramen ovale if systemic vasodilation predominates over pulmonary vasodilation. In our experience, vasodilators such as hydralazine may preserve or improve arterial oxygenation, possibly because the worsening VA/Q relationship is offset by an increased mixed venous oxygen content which results from the improved cardiac output (197).

The role of vasodilator therapy for cor pulmonale remains uncertain: While vasodilators may improve hemodynamics, the long term effects of these agents on right ventricular fraction have not yet been addressed. Kawakami et al (198) recently correlated survival in COPD with the level of mixed venous PO_2, and Bergofsky (199) suggested that, since vasodilators increase PvO_2, further studies are in order to evaluate the effects of these drugs on survival. To date, however, it is unknown whether this therapeutic approach influences survival or even improves exercise tolerance. Vasodilators should be reserved for patients who, despite an aggressive approach to conventional therapy, have persistent signs of pulmonary hypertension or right ventricular failure. Vasodilator therapy remains an investigative intervention and should be instituted only using a protocol combining hemodynamic and gas exchange monitoring, and should be performed by individuals who are experienced in such such studies.

VI. Summary

Despite advances in our understanding and treatment of respiratory diseases, cor pulmonale remains a frequent and serious complication of chronic pulmonary disease. The development and application of newer diagnostic techniques may enable the clinician to identify the presence of pulmonary hypertension in lung disease patients at an earlier, and, therefore, a more reversible stage. Therapy should be individualized for each patient based on the underlying disease and both objective and subjective responses.

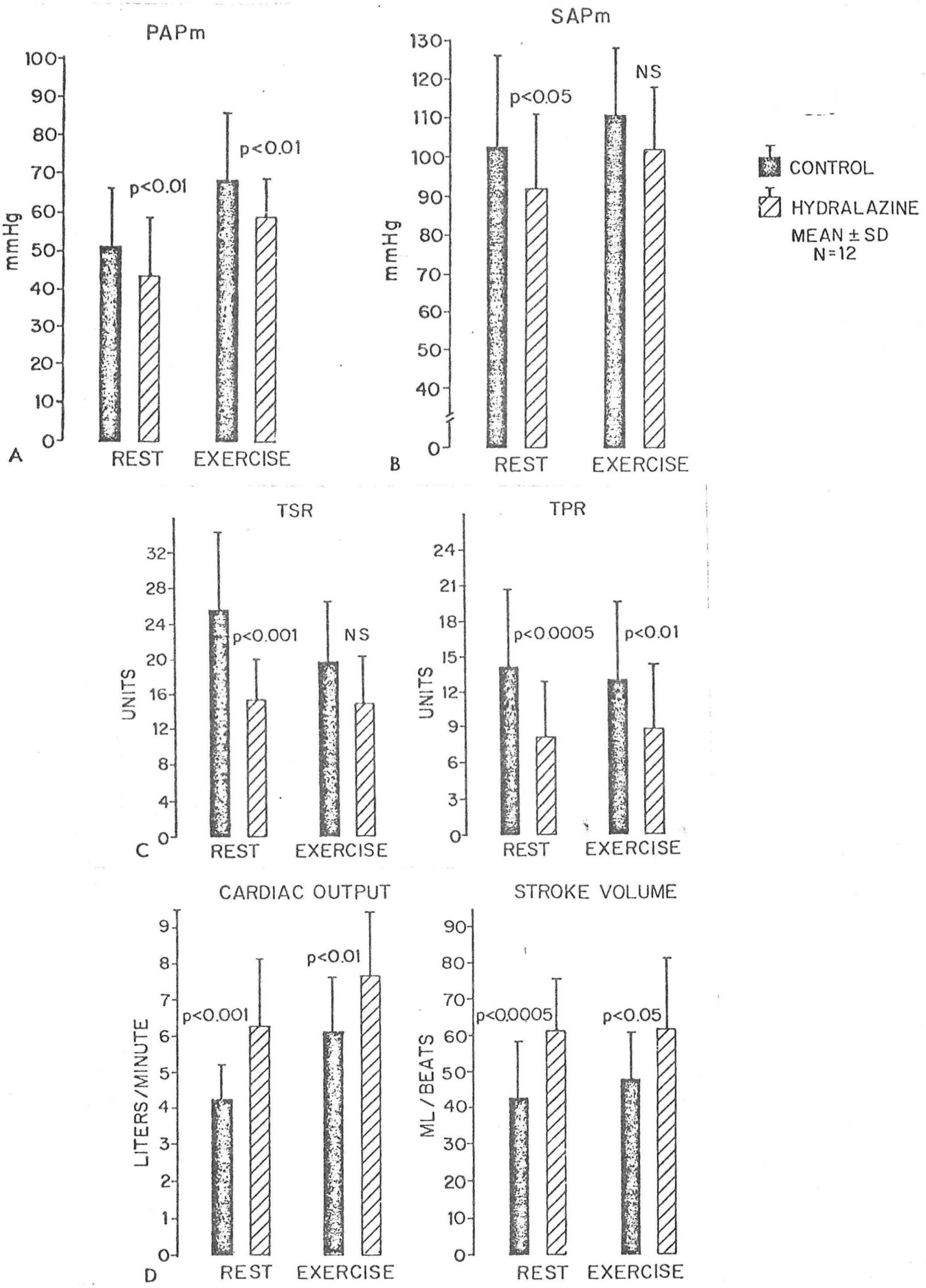

Figure 20. Effects of hydralazine in 12 cor pulmonale patients. A, mean pulmonary artery pressure (PAPm); B, mean systemic artery pressure (SAPm); c, total systemic (TSR) and total pulmonary (TPR) resistances. From ref. 189.

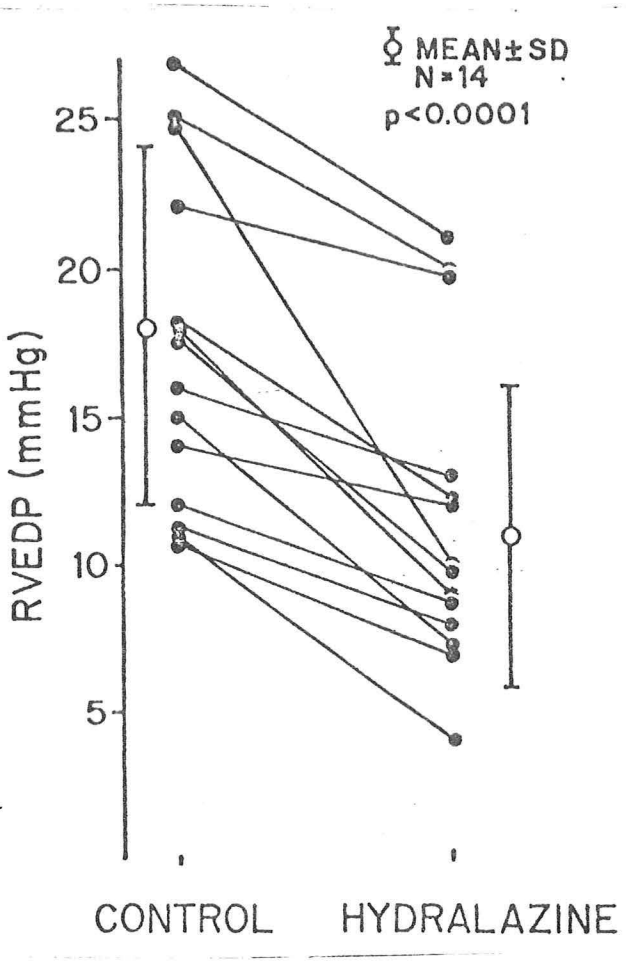

Figure 21. Right ventricular end-diastolic pressure (RVEDP) before (control) and after hydralazine 50 mg orally every 6 hours for 48 hours in 14 patients with right venticular failure. From ref. 191.

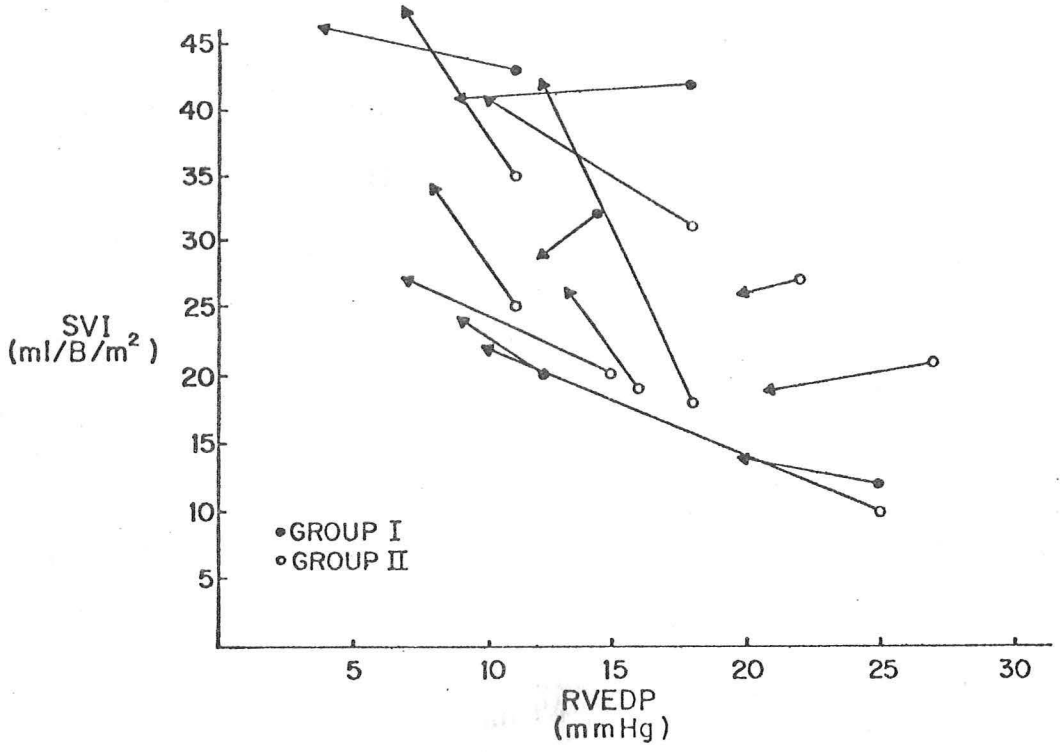

Figure 22. The relationship between right ventricular end-diastolic pressure (RVEDP) and stroke volume index (SVI) in 14 patients with RV failure treated with hydralazine. Circles represent control and arrows represent post-hydralazine measurements. Group I had reductions in mean PA pressure, while Group II did not. From ref. 191.

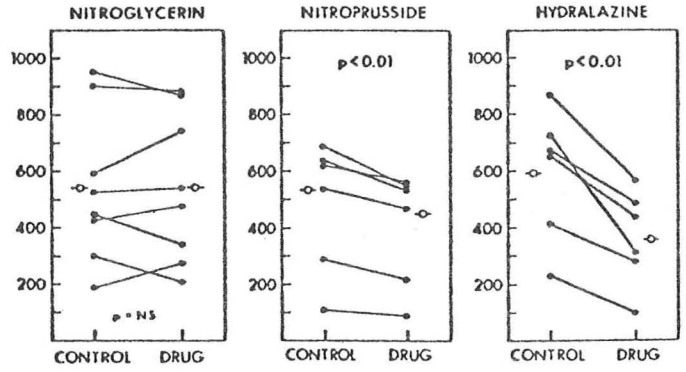

Figure 23. Pulmonary vascular resistance index (dynes sec cm^{-5}/m^2) at control and after administration of 3 vasodilators in patients with stable COPD and chronic cor pulmonale. From ref. 192.

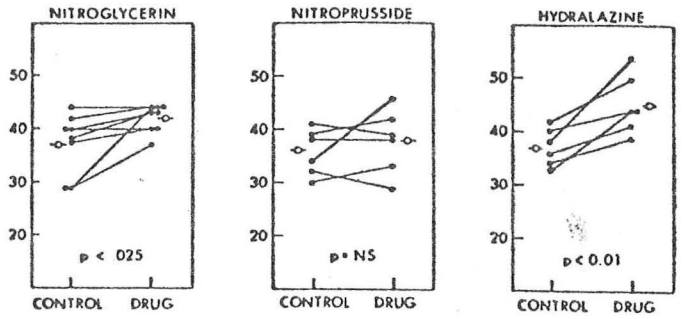

Figure 24. Right ventricular ejection fraction (percent) at control and after vasodilator administration in patients with stable COPD and cor pulmonale. From ref. 192.

Table VI. Evaluation and Use of Vasodilators for Pulmonary Hypertension

Drug Classification	Preliminary Testing	Dose Half-Life	Chronic Therapy
Beta Adrenergic Agonists			
Isoproterenol	0.5-1.0 µg/min IV, increasing by 0.5 µg/min every 5 minutes. Maximal dose 5 µg/min.	< 15 min	10 mg sublingually every 4 hours; up to 20 mg every 3 hours.
Alpha Adrenergic Antagonists			
Phentolamine	0.5 mg/min IV; maximal dose 10 mg	1-2 hours	25 mg orally every 6 hours, up to 50 mg every 3 hours.
Calcium Channel Blockers			
Nifedipine	10-20 mg sublingually	2 hours	10-40 mg orally four times a day.
Diltiazem	0.25 mg/kg IV	15-30 min.	30 mg orally three times a day.
†Nitrendipine	10-20 mg PO	6-12 hrs.	10-20 mg PO BID.
"Direct" Vasodilators			
Hydralazine	*10-20 mg IV	2-7 hrs.	25-50 mg orally every 6 hours, up to 75 mg every 6 hours.
Diazoxide	*Slow injection of 50 mg, 100 mg, 200 mg, and 300 mg. Measurements 5 minutes after each dose	> 10 hrs.	100 mg orally twice a day, up to 200 mg three times a day.
Nitrates	Nitroprusside 0.5 µg/kg/min, increasing by 0.5 µg/kg/min every 5 minutes	5-10 min.	Transdermal-nitroglycerin 2.5 mg/24 hrs., gradually increase as tolerated.
Prostaglandins			
†Prostacyclin (PGI_2)	1-2 ng/kg/min, increasing by 1-2 ng/kg/min every 15 minutes. Maximal dose 12 ng/kg/min	3-5 min.	Under investigation
†Prostaglandin E_1 (PGE_1)	0.02-0.04 µg/kg/min	< 30 min	Under investigation

* Intravenous route not recommended because of risk of systemic hypotension

† Investigational drug

References

1. Laennec RTH: A Treatise on the Diseases of the Chest and on Mediate Auscultation. Translated by J. Forbes, London, 1834.
2. Garrison FH: Contributions to the history of medicine. New York, Hafner Publications Co., 1966.
3. White PD: Heart Diseases. New York, MacMillan, 1931.
4. Chronic Cor Pulmonale: Report of an expert committee. Circulation 27: 594-615, 1963.
5. Bishop JM: Cardiovascular complications of chronic bronchitis and emphysema. Med Clin North Am 57: 771-780, 1973.
6. Neal RW, Nair KG, Hecht HH: A pathophysiological classification of cor pulmonale: with general remarks on therapy. Mod Concepts Cardiovasc Dis 37: 107-112, 1968.
7. Cornet A, Barbier JP, Debesse B, Even P, Carnot F, Neveu D: Sarcoidose avec hypertension portale et hypertension arterielle pulmonaire. Ann Med Interne 131: 431-434, 1980.
8. Battesti JP, Georges R, Basset F, Saumon G: Chronic cor pulmonale in pulmonary sarcoidosis. Thorax 33: 76-84, 1978.
9. Bunch TW, Tancredi RG, Lie JT: Pulmonary hypertension in polymyositis. Chest 79: 105-107, 1981.
10. Farber HW, Falls R, Glauser FL: Transient pulmonary hypertension from the intravenous injection of crushed, suspended pentazocine tablets. Chest 80: 178-182, 1981.
11. Robertson CH, Reynolds RC, Wilson JE: Pulmonary hypertension and foreign body granulomas in intravenous drug abusers: documentation by cardiac catheterization and lung biopsy. Am J Med 61: 657-664, 1976.
12. Harvey RM, Ferrer MI, Richards DW, Cournand A: Influence of chronic pulmonary disease on the heart and circulation. Am J Med 10: 719-738, 1951.
13. Borden CW, Wilson RH, Ebert RV, Wells HS: Pulmonary hypertension in chronic pulmonary emphysema. Am J Med 8: 701-709, 1950.
14. Heath D, Brewer D, Hicken P: Cor pulmonale in emphysema. In: Mechanisms and Pathology, Springfield, IL, Charles C. Thomas, 1968.
15. Ferrer MI: Cor pulmonale (pulmonary heart disease): Present day status. Am Heart J 89: 657-664, 1975.
16. Bishop JM: Hypoxia and pulmonary hypertension in chronic bronchitis. Prog Resp Res 9: 10-16, 1975.
17. Segel N, Bishop JM: The circulation in patients with chronic bronchitis and emphysema at rest and during exercise, with special reference to the influence of changes in blood viscosity and blood volume on the pulmonary circulation. J Clin Invest 45: 1555-1568, 1966.
18. Fishman AP: Chronic cor pulmonale. Am Rev Respir Dis 114: 775-794, 1976.
19. Thomas AJ: Chronic pulmonary heart disease. Br Heart J 34: 653-657, 1972.
20. Siassi B, Moss AJ, Dooley RR: Clinical recognition of cor pulmonale in cystic fibrosis. J Pediatr 78: 794-805, 1971.
21. Symchych PS: Pulmonary hypertension in cystic fibrosis. Arch Path 92: 409-414, 1971.
22. Moss AJ, Harper WH, Dooley RR, Murray JF, Mack JF: Cor pulmonale in cystic fibrosis of the pancreas. J Pediatr 67: 797-807, 1965.
23. "GAP" Conference Report: Cor Pulmonale. Cystic Fibrosis Foundation, Rockville, MD, 1980.

24. Llamas R, Schwartz A, Gupta SK, Baum GL: Unilateral hyperlucent lung with polycythemia and cor pulmonale. Chest 59: 690-692, 1971.
25. Crystal RG, Fulmer JD, Roberts WC, Moss ML, Line BR, Reynolds HY: Idiopathic pulmonary fibrosis. Ann Intern Med 85: 769-788, 1976.
26. Turner-Warwick M, Burrows B, Johnson A: Cryptogenic fibrosing alveolitis: Clinical features and their influence on survival. Thorax 35: 171-180, 1980.
27. Steinberg I: Cor pulmonale due to pulmonary fibrosis simulating mediastinal tumor. JAMA 199: 158-160, 1967.
28. Heath D, Gillund TD, Kay JM, Hawkins CF: Pulmonary vascular disease in honeycomb lung. J Path Bact 94: 423-430, 1968.
29. Smith LJ, Lawrence JB, Katzenstein ALA: Vascular sarcoidosis: A rare cause of pulmonary hypertension. Am J Med Sci 285: 38-44, 1983.
30. Levine BW, Saldana M, Hutter AM: Pulmonary hypertension in sarcoidosis. Am Rev Respir Dis 103: 413-417, 1971.
31. Moffat RE, Sobonya RE, Chang CHJ: Childhood sarcoidosis with fatal cor pulmonale. Pediatr Radiol 7: 180-182, 1978.
32. Lapp NL, Seaton A, Kaplan KC, Hunsaker MR, Morgan WKC: Pulmonary hemodynamics in symptomatic coal miners. Am Rev Respir Dis 104: 418-426, 1971.
33. Morgan WKC, Seaton A: Occupational Lung Disease. Philadelphia, PA, WB Saunders, 1975.
34. Wells AL: Cor pulmonale in coal workers' pneumoconiosis. Br Heart J 16: 74-78, 1954.
35. Young RH, Mark GJ: Pulmonary vascular changes in scleroderma. Am J Med 64: 998-1004, 1978.
36. Salerni R, Rodman GP, Leon DF, Shaver JA: Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). Ann Intern Med 86: 394-399, 1977.
37. Kobayashi H, Sano T, Ii K, Hizawa K, Yamanoi A, Otsuka T: Mixed connective tissue disease with fatal pulmonary hypertension. Acta Pathol Jpn 32: 1121-1129, 1982.
38. Eulderink F, Cats A: Fatal primary pulmonary hypertension in mixed connective tissue disease. Z Rheumatol 40: 25-29, 1981.
39. Jones MB, Osterholm RK, Wilson RB, Martin FH, Commers JR, Bachmayer JD: Fatal pulmonary hypertension and resolving immune-complex glomerulonephritis in mixed connective tissue disease. Am J Med 65: 855-863, 1978.
40. Perez HD, Kramer N: Pulmonary hypertension in systemic lupus erythematosus: Report of four cases and review of the literature. Semin Arth Rheum 11: 177-181, 1981.
41. Turner-Stokes L, Turner-Warwick M: Intrathoracic Manifestations of SLE. Clin Rheum Dis 8: 229-242, 1982.
42. Kay JM, Banik S: Unexplained pulmonary hypertension with pulmonary arteritis in rheumatoid disease. Br J Dis Chest 71: 53-59, 1977.
43. Gardner DL, Duthie JJR, MacLeod J: Pulmonary hypertension in rheumatoid arthritis: report of a case with intimal sclerosis of the pulmonary and digital arteries. Scott Med J 2: 183-188, 1957.
44. Jordan JD, Snyder CH: Rheumatoid disease of the lung and cor pulmonale. Am J Dis Child 108: 174-180, 1964.
45. Onodera S, Hill JR: Pulmonary hypertension. Report of a case in association with rheumatoid arthritis. Ohio State Med J 61: 141-144, 1965.
46. Case Records of the Massachusetts General Hospital. N Engl J Med 298:

327-332, 1978.
47. Basset F, Corrin B, Spencer H, Lacronique J, Roth C, Soler P, Battesti JP, Georges R, Chretien J: Pulmonary histiocytosis X. Am Rev Respir Dis 118: 811-820, 1978.
48. Adelemus LR, Lee RE: Carcinomatosis of the lung with pulmonary hypertension. Pathoradiologic spectrum. Arch Intern Med 119: 32-38, 1967.
49. Sweaney SK, Moss WT, Haddy FJ: The effects of chest irradiation on pulmonary function. J Clin Invest 38: 587-593, 1959.
50. Levy AM, Tabakin BS, Hanson JS, Narkewicz RM: Hypertrophied adenoids causing pulmonary hypertension and severe congestive heart failure. N Engl J Med 277: 506-511, 1967.
51. Jezek V, Ourednik A, Lichtenberg J, Mostecky H: Cardiopulmonary function in lung resection performed for bronchogenic cancer in patients above 65 years of age. Respiration 27: 42-50, 1970.
52. DiMaria G: The effect of pneumonectomy on the central hemodynamics. Prog Resp Res 5: 253-255, 1970.
53. Jezek V: Pulmonary hemodynamics in bronchogenic cancer before and after lung resection. Prog Resp Res 5: 237-243, 1970.
54. Penaloza D, Sime F: Chronic cor pulmonale due to loss of altitude acclimatization (chronic mountain sickness). Am J Med 50: 728-743, 1971.
55. Sime F, Banchero N, Penaloza D, Gamboa R, Cruz J, Marticorena E: Pulmonary hypertension in children born and living at high altitudes. Am J Cardiol 11: 143-149, 1963.
56. Banchero N, Sime F, Penaloza D, Cruz J, Gamboa R, Marticorena E: Pulmonary pressure, cardiac output, and arterial oxygen saturation during exercise at high altitude and at sea level. Circulation 33: 249-262, 1966.
57. Bergofsky EH, Turino GM, Fishman AP: Cardio-respiratory failure in Kyphoscoliosis. Medicine 38: 263-317, 1959.
58. Wanderman KL, Goldstein MS, Faber J: Cor pulmonale secondary to severe kyphoscoliosis in Marfan's syndrome. Chest 67: 250-251, 1975.
59. Bergofsky EH: Cor pulmonale in the syndrome of alveolar hypoventilation. Prog Cardiovasc Dis 9: 414-437, 1967.
60. Cherniack RM, Ewart WB, Hildes JA: Polycythemia secondary to respiratory disturbances in poliomyelitis. Ann Intern Med 46: 720-727, 1957.
61. Coccagna G, Mantovani M, Brignami F, Parchi C, Lugaresi E: Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnia with periodic breathing. Bull Eur Physiopathol Respir 8: 1159-1172, 1972.
62. Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC: Hemodynamics in sleep-induced apnea. Ann Intern Med 85: 714-719, 1976.
63. Guilleminault C, Tilkian A, Dement WC: The sleep apnea syndromes. Annu Rev Med 27: 465-484, 1976.
64. Guilleminault C, Eldridge FL, Simmons FB: Sleep apnea syndrome: Can it induce hemodynamic changes? West J Med 123: 7-16, 1975.
65. Mellins RB, Balfour HH, Turino GM, Winters RW: Failure of automatic control of ventilation (Ondine's Curse). Medicine 49: 487-504, 1970.
66. Lawrence LT: Idiopathic hypoventilation, polycythemia and cor pulmonale. Am Rev Respir Dis 80: 575-581, 1959.
67. Naeye RL: Alveolar hypoventilation and cor pulmonale secondary to damage to the respiratory center. Am J Cardiol 8: 416-419, 1961.

68. Voelkel NF, Reeves JT: Primary pulmonary hypertension. In: Pulmonary Vascular Diseases, Moser KM (ed), New York, Marcel Dekker, 1979, p. 573-628.
69. Lupi HE, Sanchez TG, Horwitz S, Gutierrez FE: Pulmonary artery involvement in Takayasu's arteritis. Chest 67: 69-74, 1967.
70. Celoria GC, Friedell GH, Sommers SC: Raynaud's disease and primary pulmonary hypertension. Circulation 22: 1055-1059, 1960.
71. Smekal P, Standfuss K, Rau G: Incidence of primary pulmonary hypertension after intake aminorexfumarat (Menocil). Prog Resp Res 5: 22-29, 1969.
72. Kay JM, Smith P, Heath D: Aminorex and the pulmonary circulation. Thorax 26: 272-270, 1971.
73. Heath D, Smith P: Pulmonary vascular disease. Med Clin N Amer 61: 1279-1307, 1977.
74. Houck RJ, Bailey GL, Daroca PJ, Brazda F, Johnson FB, Klein RC: Pentazocine abuse - Report of a case with pulmonary arterial cellulose granulomas and pulmonary hypertension. Chest 77: 227-230, 1980.
75. Groth DH, MacKay GR, Crable JV, Cochran TH: Intravenous injection of talc in a narcotics addict. Arch Path 94: 171-178, 1972.
76. Bainborough AR, Jericho KWF: Cor pulmonale secondary to talc granulomata in the lungs of a drug addict. Can Med Assoc J 103: 1297-1298, 1970.
77. Wedndt VE, Puro HE, Shapiro J: Angiothrombotic pulmonary hypertension in addicts: "blue velvet" addition. JAMA 188: 755-757, 1964.
78. McDonnell PJ, Toye PA, Hutchins GM: Primary pulmonary hypertension and cirrhosis: Are they related? Am Rev Respir Dis 127: 437-441, 1983.
79. Lebrec D, Capron JP, Dhumeaux D, Benhamou JP: Pulmonary hypertension complicating portal hypertension. Am Rev Respir Dis 120: 849-856, 1979.
80. Adam A, Patterson DLH: Pulmonary hypertension associated with hepatic cirrhosis and primary acrocyanosis. J R Soc Med 74: 689-691, 1981.
81. Kibria G, Smith P, Heath D, Sagar S: Observations on the rare association between portal and pulmonary hypertension. Thorax 35: 945-949, 1980.
82. Clinicopathologic Conference: Chronic active hepatitis and pulmonary hypertension. Am J Med 63: 604-613, 1977.
83. Ruttner JR, Bartschi JP, Niedermann R, Schnieder J: Plexogenic pulmonary arteriopathy and liver cirrhosis. Thorax 35: 133-136, 1980.
84. Cohen MD, Rubin LJ, Taylor WE, Cuthbert JA: Primary pulmonary hypertension - A unique case associated with extrahepatic portal hypertension. Hepatology 3(4): 588-592, 1983.
85. Senior RM, Britton RC, Turino GM, Wood JA, Langer GA, Fishman AP: Pulmonary hypertension associated with cirrhosis of the liver and with portacaval shunts. Circulation 37: 88-96, 1968.
86. Eldredge WJ, Tinglestaad JB, Robertson LW, Mauck HP, McCue CM: Observations on the natural history of pulmonary arterial coarctations. Circulation 45: 404-409, 1972.
87. Collins FS, Orringer EP: Pulmonary hypertension and cor pulmonale in the sickle hemoglobinopathies. Am J Med 73: 814-821, 1982.
88. Rowley PT, Enlander D: Hemoglobin S-C disease presenting as acute cor pulmonale. Am Rev Respir Dis 98: 494-500, 1968.
89. Levin DL, Weinberg AG, Perkin RM: Pulmonary microthrombi syndrome in newborn infants with unresponsive persistent pulmonary hypertension. J Pediatr 102: 299-303, 1983.
90. Paraskos JA, Adelstein SJ, Smith RE, Rickman FD, Grossman W, Dexter L,

Dalen JE: Late prognosis of acute pulmonary embolism. N Engl J Med 289: 55-58, 1973.
91. Wilhelmsen L, Selander S, Soderholm B, Paulin S, Varnauskas E, Werko L: Recurrent pulmonary embolism. Medicine 42: 335-355, 1963.
92. Riedel M, Stanek V, Widimsky J, Prerovsky I: Long term follow-up of patients with pulmonary thromboembolism. Chest 81: 151-158, 1982.
93. Fleischner FG: Recurrent pulmonary embolism and cor pulmonale. N Engl J Med 276: 1213-1220, 1967.
94. Owen WR, Thomas WA, Castleman B: Unrecognized emboli to the lungs with subsequent cor pulmonale. N Engl J Med 249: 919-926, 1953.
95. Dalen JE, Alpert JS: Natural history of pulmonary embolism. Prog Cardiovasc Dis 17: 259-270, 1975.
96. Falicox RE, Resnekov L, Petasnick J: Progressive pulmonary vascular obstruction and cor pulmonale due to repeated embolism from axillary vein thrombosis. Ann Intern Med 73: 429-431, 1970.
97. Heath D, MacKinnon J: Pulmonary hypertension due to myxoma of the right atrium, with special reference to the behavior of emboli of myxoma in the lung. Am Heart J 68: 227-235, 1964.
98. Marini JJ, Bilnoski W, Huseby JS: Acute cor pulmonale resulting from tumor microembolism. West J Med 132: 77-80, 1980.
99. Graham JP, Rotman HH, Weg JG: Tumor emboli presenting as pulmonary hypertension. Chest 69: 229-230, 1976.
100. Vitale JCG, Bunuel RC: Pulmonary tumor emboli and cor pulmonale in primary carcinoma of the lung. Cancer 38: 2105-2110, 1976.
101. Chakeres DW, Spiegel PK: Fatal pulmonary hypertension secondary to intravascular metastatic tumor emboli. Amer J Roentgen 139: 997-1000, 1982.
102. Mendelson CL: Acute cor pulmonale and pregnancy. Clin Obstet Gynecol 11: 992-1009, 1968.
103. Obeyesekere I, Peiris D: Pulmonary hypertension and filariasis. Br Heart J 36: 676-681, 1974.
104. Marchand E, Marcial-Rojas R, Rodriguez R, Polanco G, Diaz-Rivera RS: The pulmonary obstruction syndrome in schistosoma mansoni pulmonary endarteritis. Report of five cases. Arch Intern Med 100: 965-980, 1957.
105. Cheris DN, Dadey JL: Fibrosing mediastinitis. An unusual cause for cor pulmonale. Amer J Roentgen 100: 328-331, 1967.
106. Nelson WP, Lundberg GD, Dickerson RB: Pulmonary artery obstruction and cor pulmonale due to chronic fibrous mediastinitis. Amer J Med 38: 279-284, 1965.
107. Arnett N, Bacos JM, Macher AM, Marsh HB, Savage DD, Fulmer JD, Roberts WC: Fibrosing mediastinitis causing arterial hypertension with pulmonary venous hypertension. Clinical and necropsy observations. Amer J Med 63: 634-643, 1977.
108. Fulton RM: The heart in chronic pulmonary disease. Q J Med 22: 43-58, 1953.
109. Flint FJ: Cor pulmonale. Lancet 2: 51-58, 1954.
110. Robin ED, Gaudio R: Cor pulmonale. Disease-A-Month, Chicago, Year Book Publishers, 1970.
111. Behnke RH, Bristow JD, Carrieri V, Pierce JA, Sasahara A, Soffer A: Resources for the optimal care of acute respiratory failure. Circulation 43: A-185-A-195, 1971.

112. U.S. Department of Health and Human Services, National Heart, Lung and Blood Institute: Division of Lung Diseases Program Report: p. 121, 1980.
113. Intersociety Commission for Heart Disease Resources: Primary prevention of pulmonary heart disease. Circulation 41: A-17, 1970.
114. Burrows B, Kettel LJ, Niden AH, Rabinowitz M, Diener CF: Patterns of cardiovascular dysfunction in chronic obstructive lung disease. N Engl J Med 286: 912-917, 1972.
115. Bishop JM: Hypoxia and pulmonary hypertension in chronic bronchitis. Prog Resp Res 9: 10-16, 1975.
116. Traver GA, Cline MG, Burrows B: Predictors of mortality in chronic obstructive pulmonary disease. Am Rev Respir Dis 119: 895-902, 1979.
117. Riley RL, Himmelstein A, Motley HL, Weiner HM, Cournand A: Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. Am J Physiol 152: 372-382, 1948.
118. Mohsenifar Z, Tashkin DP, Levy SE, Bjerke RD, Clements PJ, Furst D: Lack of sensitivity of measurements of VD/VT at rest and during exercise in detection of hemodynamically significant pulmonary vascular abnormalities in collagen vascular disease. Am Rev Respir Dis 123: 508-572, 1981.
119. Widimsky J, Riedel M, Stanek V: Central hemodynamics during exercise in patients with restrictive pulmonary disease. Bull Europ Physiopath Resp 13: 369-379, 1977.
120. Fishman AP: Dynamics of the pulmonary circulation. In: Handbook of Physiology, Section 2, Washington DC, American Physiology Society, 1963.
121. Von Euler US, Liljestrand G: Observations on the pulmonary arterial blood pressure in the cat. Acta Physiol Scand 12: 301-320, 1946.
122. Barer GS, Howard P, Shaw JW: Stimulus-response curves for the pulmonary vascular bed to hypoxia and hypercapnia. J Physiol (London) 211: 139-155, 1970.
123. Barer GR, McCurrie JR, Shaw JW: Effect of changes in blood pH on the vascular resistance of normal and hypoxic cat lung. Cardiovasc Res 5: 490-497, 1971.
124. Harvey RM, Enson Y, Betti R, Lewis ML, Rochester DF, Ferrer MI: The influence of hydrogen ion concentration and hypoxia on the pulmonary circulation. J Clin Invest 43: 1146-1162, 1964.
125. Kilburn KH, Asmundsson T, Britt RC, Cardon R: Effects of breathing 10 percent carbon dioxide on the pulmonary circulation of human subjects. Circulation 39: 639-653, 1969.
126. Fishman AP: Respiratory gases in the regulation of the pulmonary circulation. Physiol Rev 41: 214-280, 1961.
127. Fishman AP: Hypoxia on the pulmonary circulation. Circ Res 38: 221-231, 1975.
128. Harris P, Segal N, Green I, Housley E: The influence of the airways resistance and alveolar pressure on the pulmonary vascular resistance in chronic bronchitis. Cardiovasc Res 2: 84-92, 1968.
129. Hyman AL, Higashida RT, Spannhake EW, Kadowitz PJ: Pulmonary vasoconstrictor responses to graded decreases in precapillary blood pO_2 in intact-chest cat. J Appl Physiol 51: 1009-1016, 1981.
130. Benumof JL, Pirlo AF, Johanson I, Trousdale FR: Interaction of PVO_2 with PAO_2 on hypoxic pulmonary vasoconstriction. J Appl Physiol 51: 871-874, 1981.
131. Hughes JD, Rubin LJ: The relationship between mixed venous oxygen tension and pulmonary vascular tone in dogs during normoxic, hyperoxic, and hypoxic

ventilation, submitted.
132. McGrath RL, Weil JV: Adverse effects of normovolemic polycythemia and hypoxia on hemodynamics in the dog. Circ Res 43: 793-798, 1978.
133. Field S, Kelly Sm, Macklem PT: The oxygen cost of breathing in patients with cardiorespiratory disease. Am Rev Respir Dis 126: 9-13, 1982.
134. Wynne JW, Block AJ, Hemenway J, Hunt LA, Flick MR: Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive lung disease (COLD). Am J Med 66: 573-579, 1979.
135. Scott RW, Garvin CF: Cor Pulmonale: Observations in fifty autopsy cases. Am Herat J 22: 56-63, 1941.
136. Michelson N: Bilateral ventricular hypertrophy due to chronic pulmonary disease. Dis Chest 38: 435-446, 1960.
137. Fluck DC, Chandrasekar RG, Gardner RV: Left ventricular hypertrophy in chronic bronchitis. Br Heart J 28: 92-97, 1966.
138. Baum GL, Schwartz A, Llamas R, Castillo C: Left ventricular function in chronic obstructive lung disease. N Engl J Med 285: 361-365, 1971.
139. Cudkowicz L, Armstrong JB: The bronchial arteries in pulmonary emphysema. Thorax 8: 46-58, 1953.
140. Roosenberg JG, Deenstra H: Bronchial-pulmonary vascular shunts in chronic pulmonary infections. Dis Chest 26: 664-671, 1954.
141. Shaw DB, Grover RF, Reeves JT, Blount SG, Jr.: Pulmonary circulation in chronic bronchitis and emphysema. Br Heart J 27: 674-683, 1965.
142. Weber KT, Janicki JS, Shroff S, Fishman AP: Contractile mechanics and interaction of the right and left ventricles. Am J Cardiol 47: 686-695, 1981.
143. Summer WR, Permutt S, Sagawa K, Shoukas AA, Bromberger-Barnea B: Effects of spontaneous respiration on canine left ventricular function. Circ Res 45: 719-728, 1979.
144. Frank MJ, Weisse AB, Moschos CB, Levinson GE: Left ventricular function, metabolism and blood flow in chronic cor pulmonale. Circulation 47: 798-806, 1973.
145. Davies H, Overy HR: Left ventricular function in cor pulmonale. Chest 58: 8-14, 1970.
146. Khaja F, Parker JO: Right and left ventricular performance in chronic obstructive lung disease. Am Heart J 82: 319-327, 1971.
147. Steele P, Ellis JH, Van Dyke D, Sutton F, Creagh E, Davies H: Left ventricular fraction in severe chronic obstructive airways disease. Am J Med 59: 21-28, 1975.
148. Murphy ML, Adamson J, Hutcheson F: Left ventricular hypertrophy in patients with chronic bronchitis and emphysema. Ann Intern Med 81: 307-313, 1974.
149. Phillips RW: The electrocardiogram in cor pulmonale secondary to pulmonary emphysema: A study of 18 cases proved by autopsy. Am Heart J 56: 352-371, 1958.
150. Kilcoyne MM, Davis AL, Ferrer MI: A dynamic electrocardiographic concept useful in the diagnosis of cor pulmonale. Circulation 42: 903-924, 1970.
151. Ferrer MI: Clinical and electrocardiographic correlations in pulmonary heart disease (cor pulmonale). Cardiovasc Clinics 8: 215-224, 1977.
152. Wilson JR, Mason UG, Bahler RC, Chester EH, Picken JJ, Baum GL: Vectorcardiographic detection of early hemodynamic abnormalities in chronic obstructive pulmonary disease. Chest 76: 160-165, 1979.
153. Nanda NC, Gramiak R, Robinson TI, Shah PM: Echocardiographic evaluation

of pulmonary hypertension. Circulation 50: 575-581, 1974.
154. Acquatella H, Schiller NB, Sharpe DN, Chatterjee K: Lack of correlation between echocardiographic pulmonary valve morphology and simultaneous pulmonary arterial pressure. Am J Cardiol 43: 946-950, 1979.
155. Boyd MJ, Williams IP, Turton CWG, Brooks N, Leech G, Millard FJC: Echocardiographic method for the estimation of pulmonary artery pressure in chronic lung disease. Thorax 35: 914-919, 1980.
156. Berger HJ, Matthay RA, Loke J, Marshall RC, Gottschalk A, Zaret B: Assessment of cardiac performance with quantitative radionuclide angiocardiography: Right ventricular fraction with reference to findings in chronic obstructive pulmonary disease. Am J Cardiol 41: 897-905, 1978.
157. Enson Y: Pulmonary heart disease: Relation of pulmonary hypertension to abnormal lung structure and function. Bull NY Acad Med 53: 551-566, 1977.
158. Timsit G, Neukirch F, du Perron MC, Verdier F, Drutel P, Legrand M, Botto MJ, Lesorbe R: Statistical correlation between PAP, spirographic data and arterial and mixed venous blood gases in 22 subjects with chronic obstructive lung disease. Prog Resp Res 9: 105-111, 1975.
159. Ferrer MI: Disturbances in the circulation in patients with cor pulmonale. NY Bull Acad Med 41: 942-958, 1965.
160. Parker JO, Kelkar K, West RO: Hemodynamic effects of aminophylline in cor pulmonale. Circulation 33: 17-25, 1966.
161. Barer GR, Gunning AJ: Action of a sympathomimetic drug and of theophylline ethylene diamine on the pulmonary circulation. Circ Res 7: 383-389, 1979.
162. Weisse AB, Moschos CB, Frank MJ, Levinson GE, Cannilla JE, Regan TJ: Hemodynamic effects of staged hematocrit reduction in patients with stable cor pulmonale and severely elevated hematocrit levels. Am J Med 58: 92-98, 1975.
163. Chetty KG, Brown SE, Light RW: Improved exercise tolerance of the polycythemic lung patient following phlebotomy. Am J Med 74: 415-420, 1983.
164. Erickson AD, Golden WA, Claunch BC, Donat WE, Kaemmerle JT: Acute effects of phlebotomy on right ventricular size and performance in polycythemic patients with chronic obstructive pulmonary disease. Am J Cardiol 52: 163-166, 1983.
165. British Medical Research Council Working Party: Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1: 681-685, 1981.
166. Nocturnal Oxygen Therapy Trial Group: Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 93: 391-398, 1980.
167. Ashtosh K, Mead G, Dunsky M: Early effects of oxygen administration and prognosis in chronic obstructive pulmonary disease and cor pulmonale. Am Rev Respir Dis 127: 399-404, 1983.
168. Boysen PG, Block AJ, Wynne JW, Hunt LA, Flick MR: Nocturnal pulmonary hypertension in patients with chronic obstructive pulmonary disease. Chest 76: 536-542, 1979.
169. DeMarco FJ, Wynne JW, Block AJ, Boysen PG, Taasan VC: Oxygen desaturation during sleep as a determinant of the "blue and bloated" syndrome. Chest 79: 621-625, 1981.
170. Bishop JM: Hypoxia and pulmonary hypertension in chronic bronchitis. Prog Resp Res 9: 10-16, 1975.

171. Anderson PB, Campbell RHA, Brennan SR, Howard P: The problem of pulmonary hypertension in chronic cor pulmonale. Prog Resp Res 9: 37-40, 1975.
172. Green LH, Smith TW: The use of digitalis in patients with pulmonary disease. Ann Intern Med 87: 459-465, 1977.
173. Ferrer MI, Harvey RM, Cathcart RT, Webster CA, Richards DW, Cournand A: Some effects of digoxin upon the heart and circulation in man: Digoxin in chronic cor pulmonale. Circulation 1: 161-186, 1950.
174. Howarth S, McMichael J, Sharpey-Schafer EP: Effects of oxygen, venesetion and digitalis in chronic heart failure from disease of the lungs. Clin Sci 6: 187-196, 1948.
175. Jezek V, Schrijen F: Hemodynamic effect of deslanoside at rest and during exercise in patients with chronic bronchitis. Br Heart J 35: 2-8, 1973.
176. Mathur PN, Powles P, Pugsley SO, McEwan MP, Campbell EJM: Effect of digoxin on right ventricular function in severe chronic airflow obstruction. Ann Intern Med 95: 283-288, 1981.
177. Noble NIM, Trenchard D, Guz A: The value of diuretics in respiratory failure. Lancet 2: 257-260, 1966.
178. Whitman V, Stern RC, Bellet P, Doershuk CF, Liebman J, Boat TF, Borkat G, Matthews LW: Studies on cor pulmonale in cystic fibrosis. I. Effects of diuresis. Pediatrics 55: 83-85, 1975.
179. Heinemann HO: Right-sided heart failure and the use of diuretics. Am J Med 64: 367-370, 1978.
180. Bear R, Goldstein M, Phillipson E, Ho M, Hammeke H, Feldman R, Handelsman S, Halperin M: Effect of metabolic alkalosis on respiratory function in patients with chronic obstructive lung disease. Canad Med Assoc J 117: 900-903, 1977.
181. Heinemann HO, Goldring RM: Bicarbonate and the regulation of ventilation. Am J Med 57: 361-370, 1974.
182. Campbell EJM, Short DS: The cause of oedema in "cor pulmonale". Lancet 1: 1184-1186, 1960.
183. Rubin LJ: Cardiovascular effects of vasodilator therapy for pulmonary arterial hypertension. Clin Chest Med 4: 309-319, 1983.
184. Peter RH, Rubin LJ: Pharmacological Control of the Pulmonary Vascular Bed. In: Advances in Internal Medicine, G.H. Stollerman, ed., 1983, in press.
185. Williams JF, White DH, Behnka RH: Changes in pulmonary hemodynamics produced by isoproterenol infusion in emphysematous patients. Circulation 28: 396-403, 1963.
186. Lockhart A, Lissac J, Salmon D, Zappacosta C, Benismail M: Effects of isoproterenol on the pulmonary circulation in obstructive airways disease. Clin Sci 32: 177-187, 1967.
187. Van Mieghem W, de Bakcer G, de Wispehere B, Biliet L, Cosemans J: Phentolamine infusion in cor pulmonale due to chronic obstructive pulmonary disease. Acta Cardiologica 4: 253-262, 1978.
188. Gould L, DeMartino A, Gomprecht RF, Umali F, Michael A: Hemodynamic effects of phentolamine in cor pulmonale. J Clin Pharm 12: 153-157, 1972.
189. Rubin LJ, Peter RH: Hemodynamics at rest and during exercise after oral hydralazine in patients with cor pulmonale. Am J Cardiol 47: 116-122, 1981.
190. Chappell TR, Rubin LJ, Markham RV, Firth BG: Independence of oxygen consumption and systemic oxygen transport in patients with either stable pulmonary hypertension or refractory left ventricular failure. Am Rev Respir Dis 128: 30-33,

1983.
191. Rubin LJ, Handel F, Peter RH: The effects of oral hydralazine on right ventricular end-diastolic pressure in patients with right ventricular failure. Circulation 65: 1369-1373, 1982.
192. Brent B, Berger H, Mahler D, Matthay R, Mahler D, Pytlik L, Zaret B: Contrasting acute effects of vasodilators (nitroglycerin, nitroprusside, and hydralazine) on right ventricular performance in patients with chronic obstructive pulmonary disease and pulmonary hypertension: A combined radionuclide-hemodynamic study. Am J Cardiol 51: 1682-1689, 1983.
193. Chappell TR, Rubin LJ, Caldwell EJ: The hemodynamic effects of chronic oral hydralazine therapy in patients with cor pulmonale. Am Rev Respir Dis 127: 81, 1983.
194. Simmoneau G, Escourrou P, Duroux P, Lockhart A: Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. N Engl J Med 304: 1582-1585, 1981.
195. Kochukoshy KN, Chick TW, Jenne JW: The effect of nitroglycerin in gas exchange on chronic obstructive pulmonary disease. Am Rev Respir Dis 111: 177-183, 1975.
196. Naeije R, Melot C, Mols P, Hallemans R: Effects of vasodilators on hypoxic pulmonary vasoconstriction in normal man. Chest 82: 404-410, 1982.
197. Miller MJ, Chappell TR, Cook W, DeOlazabol JR, Rubin LJ: Effects of oral hydralazine on gas exchange in patients with cor pulmonale. Am J Med 1983, in press.
198. Kawakami Y, Kishi F, Yamamoto H, Miyamoto K: Relation of oxygen delivery, mixed venous oxygenation, and pulmonary hemodynamics to prognosis in chronic obstructive pulmonary disease. N Engl J Med 308: 1045-1049, 1983.
199. Bergofsky EH: Tissue oxygen delivery and cor pulmonale in chronic obstructive pulmonary disease (Editorial). N Engl J Med 308: 1092-1094, 1983.