

The Pathophysiology Of Pulmonary Hypertension

ISAAC BONIUK '62

For the student in the early years of medicine, no general topic points out his inadequate knowledge more than does pulmonary physiology and function. At best, any acquaintance with the topic is in knowing a few isolated but ill-understood terms, and this poor background works in a vicious circle to ensure that this state will continue. Part of the reason for his lack of knowledge, no doubt, lies in the fact that much of the available data is supported by diverse and hard to prove theories, and the budding student is soon as confused as are many of his more senior colleagues. When I first thought of the topic of pulmonary hypertension for this paper, I did so because I felt it would enable me to correlate some of the aspects of cardiac and of pulmonary function; however, I must admit that though I had heard the term used on many occasions, I neither understood its full meaning, nor was I aware, to any extent, of its clinical significance.

I shall attempt to cover the topic by defining my terms and giving a classification which can be easily followed, then commenting on some of the general features of pulmonary hypertension, some evidence of its pathological sequelae, and some of the hemodynamics which accompany certain specific disease processes.

The term pulmonary hypertension is commonly used to denote arterial hypertension, but the importance of pulmonary venous hypertension must not be forgotten, and some authors suggest qualifying pulmonary hypertension with the appropriate adjective, arterial or venous. By definition, pulmonary arterial hypertension exists when the pulmonary artery pressure exceeds the maximum normal limit, defined by Wood as 30/15 mm. of mercury, measured from the sternal angle, the maximum normal mean pressure being 22 mm. of mercury. The main factors maintaining pulmonary arterial pressure are right ventricular output, and resistance to flow offered by the pulmonary vascular bed.

CLASSIFICATION

1. Hyperdynamic—Increased pulmonary flow
—Low pulmonary resistance
2. Obstructive—Increased pulmonary resistance
—Low pulmonary flow
 - a. Passive
 - b. Vasoconstrictive
 - c. Obliterative

This classification is modified from that of Paul Wood, who would undoubtedly prefer the term 'hyperkinetic' to 'hyperdynamic' pulmonary hypertension. Hyperkinetic pulmonary hypertension best describes a high pulmonary artery pressure caused chiefly by increased blood flow (hyperkinetic has long been used to describe a high cardiac output, and kinetic refers to movement, while dynamic refers to force. Hyperdynamic pulmonary hypertension would mean that a raised pulmonary artery pressure was caused primarily by more forceful contraction of the right ventricle, a situation that does not exist). Heretofore, I shall use the term 'hyperkinetic' in preference to 'hyperdynamic' pulmonary hypertension.

1. *Hyperkinetic Pulmonary Hypertension*

This occurs when the pulmonary blood flow is increased past the limit of elasticity of the pulmonary vascular bed. Up to three times the resting cardiac output can be accommodated without a rise in pressure, so only with a flow greater than 15 Liters/min. does the pressure rise. Examples of this are—severe anemia, multiple arteriovenous

fistulae, Paget's disease of bone, hyperthyroidism, cor pulmonale, hepatic disease, protracted vitamin B deficiency, and congenital heart disease with left to right shunt. In the last example, the hypertension may be aggravated by vaso-constrictive obliterative changes.

2. *Obstructive Pulmonary Hypertension*

This results from a lesion which increases the resistance to flow, and hinders blood from entering or leaving the pulmonary vascular bed. It includes lesions of the left ventricle, left atrium, and pulmonary veins, capillaries, and arterioles.

a. *Passive*—Elevated pressures in the left side of the heart are transmitted to the pulmonary artery. This occurs in mitral stenosis, tumors of the left atrium, and in left ventricular failure.

b. *Vasoconstrictive*—A number of factors are believed to precipitate the arteriolar constriction. Some of these are drugs, decreased oxygen tension of the pulmonary arterial blood, antecedent pulmonary venous hypertension, and prolonged and excessive pulmonary blood flow in certain cases of congenital heart disease. Pulmonary arterial hypertension, in itself, tends to provoke vasoconstriction.

Some further comments will enlarge on the above statements. The mechanism by which hypoxia produces vasoconstriction has not been proved, and sympathetic denervation has failed to settle whether the mechanism is reflex or direct. The practical applications of hypoxic vasoconstriction are important in understanding how pulmonary heart failure can so easily result from lung infections which impair ventilation and respiratory exchange, and why oxygen is so important in treatment of these conditions.

Many drugs have an effect upon the pulmonary circulation, but deductions as to their mode of action are misleading because of the many variables which cannot be controlled. A drug that lowers pulmonary artery pressure, for instance, may in reality be doing so not by dilatation of the vasculature, but by increasing the cardiac output and thus reducing the pulmonary venous pressure.

Where there is a progressive pulmonary venous hypertension, as in mitral stenosis, the pulmonary artery pressure rises linearly until the left atrial pressure approximates 20-25 mm. of mercury. Then there is a sudden rise in pulmonary arterial pressure, quite beyond that which would be due to mere passive increase. This is active arterial hypertension, which might be due to vasoconstriction or to organic occlusive changes in the arterioles, or to both. Evidence seems to favor pulmonary vasoconstriction as the prime cause. Bayliss and co-workers showed that pulmonary arterial pressure can increase with heart failure and decrease with recovery, suggesting a reversible

Compliments of

BELTONE OF THE MARITIMES

11½ PRINCE STREET -:- HALIFAX, N. S.

Telephone 423-8817

A full range of Hearing Aids and Audiometers available.

Technical specifications supplied on request.

process, such as vasoconstriction. Further evidence for vasoconstriction comes from acute studies with drugs and other agents.

c. *Obliterative*—The major cause is thromboembolic phenomena, but bilharzial disease, arteritides such as periarteritis nodosa, and compromise of the vascular bed as in pulmonary fibrosis and emphysema, are included. This type of pulmonary hypertension, carries with it the worst prognosis.

The distinction should always be made between venous and arterial hypertension, though it must be remembered that preceding venous hypertension is one of the common causes of arteriolar vasoconstriction, and the two can co-exist, as they so often do, in mitral stenosis.

CLINICAL FEATURES

When hypertension is due to high pulmonary blood flow, the patient may have few symptoms (other than dyspnea on exertion) apart from those due to the condition responsible for the high rate of flow. The patient will have a full, bounding pulse, the jugular venous pressure will be increased, and the extremities warm and moist. The cardiac impulse will be increased, and heart may be enlarged. Pulmonary and aortic ejection murmurs will be heard with accentuation of the second heart sound. Other physical signs will depend on the underlying disease process. When the increased pulmonary blood flow is due to a left to right shunt in congenital heart disease, the signs of high cardiac output are absent, for the left ventricular output is normal or reduced. When the primary cause for the hyperkinetic circulation is corrected, the pulmonary artery pressure will return to normal.

When the pulmonary vascular resistance is raised, the cardiac output tends to fall—yielding a different clinical picture. The complaints will include extreme fatigue, especially on exertion, with dyspnea, and a loss of consciousness may result after, or on,

— Compliments of —

J. F. HARTZ CO. LTD.

107 MORRIS STREET

HALIFAX, N. S.

PHONE 423-7172

Suppliers of:

Welch Allyn Diagnostic Instruments

Stille Surgical Instruments (made in Sweden)

other high quality surgical equipment

exercise, due to the inadequate cardiac output under the extra burden of the exercise. Angina will also be a complaint even though the coronary arteries may be normal. The patient will tend to be underweight, with an anxious mien, a malar flush, and cold, pale extremities. A presystolic murmur, heard best over the right side of the heart is indicative of right atrial hypertrophy. The first sound is followed by an early systolic click, and a short ejection murmur due to blood entering the dilated pulmonary artery under high pressure. If the right ventricular hypertension is very great, yielding tricuspid incompetence, a pansystolic murmur will be heard. All of these signs, however, are not present unless the arterial hypertension is extreme.

DIAGNOSIS

The diagnosis can be anticipated on the clinical findings, but cardiac catheterization and radiography will be required to ensure the diagnosis. Once the diagnosis is made, the cause can be sought by noting evidence of the hyperkinetic state, the severe dyspnea, especially paroxysmal, suggestive of venous hypertension, or the tiredness, fainting, and anginal pain suggestive of a high arteriolar resistance. If evidence of pulmonary venous hypertension is lacking, then the obstruction lies in the arteriolar bed, and the cause may be chronic lung disease, thromboembolism, pulmonary arteritis, or idiopathic pulmonary hypertension.

MANAGEMENT

Surgery offers the best results in the vasoconstrictive and hyperkinetic types, as by closure of a septal defect, or a mitral valvotomy. For vasoconstriction due to hypoxia induced by disease of the lung parenchyma, judiciously applied oxygen therapy will increase the arterial saturation and decrease the vasoconstriction; antibiotics and bronchodilators will aid in restoring normal pulmonary function. Although drugs generally are of little help, aminophylline, because of its ability to lower the pulmonary arteriolar resistance, its cardiotoxic and bronchodilator effects, may be an exception to this generality. In arteritis, cortisone or one of its analogues may be of aid. In thromboembolism, long-term or permanent anticoagulants may be required. In patients with obliteration or obstruction from other causes than thromboembolic phenomena, anticoagulants may be of help in preventing the onset of thrombosis because of sluggish blood flow through the diseased pulmonary vessels. However, if the process of obliterative hypertension becomes progressive, there is little else than resorting to digitalis, low salt diet, and diuretics. At the present time, therefore, hyperkinetic and vasoconstrictive hypertension have a good prospect of relief by surgical means, if not delayed and irreversible changes have occurred. Obliterative hypertension is virtually untreatable, except by anticoagulants, which may be combined with one or more vasodilators in the hope that the progress of the disease may be halted.

THE BOOK ROOM LIMITED

"Everything in Books"

P. O. Box 272

HALIFAX, NOVA SCOTIA

Phone 423-8271

PROGNOSIS

The prognosis depends on the underlying disease, and the state of the pulmonary vascular bed. Left to right shunts can be treated by closure of the septal defect, and in high output states such as thyrotoxicosis returning the patient to a normal cardiac output, as for example, by rendering him euthyroid, will restore the pulmonary circulation to its normal physiological state. Similarly, mitral valvotomy will reduce the pulmonary venous hypertension, but must be done before secondary irreversible vasoconstrictive effects are superimposed. Where the pulmonary vascular bed is obliterated, or the lung parenchyma severely damaged, the prognosis is grave, and progressive right ventricular failure and death will result in a matter of months. Whatever the cause, the prognosis varies directly with the severity of the hypertension. Also, since irreversible changes in the pulmonary vessels occur as a result of prolonged hyperkinetic and vasoconstrictive hypertension, with secondary pulmonary vascular obstruction, the duration of the pulmonary hypertension is important.

PATHOLOGY

Vascular changes vary with the severity of the disease. In all forms of pulmonary hypertension, there is an increased incidence or severity of atheroma (typically, in pulmonary atheroma, the plaques are hardly elevated above the level of the surrounding intima). An increase in the muscular fibres of the media has been noted and in the smallest elastic arteries, the muscular arteries, and the arterioles, intimal fibrosis and medial necrosis are seen. In the veins as well, there is some medial muscular hypertrophy with increase in the surrounding connective tissue (this latter finding probably due to chronic lymphatic distension, or edema). As the severity of the pulmonary hypertension increases, the atheroma formation becomes more elevated and the plaques resemble those found in the systemic circulation. Furthermore, the

Best Wishes To

**The
Dalhousie Medical Society**

**National-Canadian Drugs
Limited**

14 Sackville Street

Telephone 423-9291

Sydney, N. S. Halifax, N.S. Saint John, N. B.

Compliments of

Henry Birks & Sons (Mar.) Ltd.

QUALITY JEWELLERS



493 Barrington St. - Halifax, N. S.

atheroma may be complicated by superimposed thrombosis. Arterial occlusion by these thromboses can yield pulmonary infarcts and thus, pleural effusion with lung collapse, and since this decreases the blood flow through the affected part, an additional strain on the right ventricle is imposed.

Certain changes are peculiar to certain conditions. In mitral stenosis, congestion, Kerley's lines, and ossification are noted. The congestion need not be marked, and the more common finding of focal siderosis is noticed. The septal lines (of Kerley) are thin straight lines of opacity seen on the X-Ray, and are due to widening of the interlobular fissures from the distension of the lymphatic vessels within them. These lines show up mainly at the periphery, because there, they lie in a plane in which they can cast a shadow. The small foci of pulmonary ossification are seen only in a minority of cases, and are believed to form as a result of sub-clinical pulmonary edema.

In a study of lungs from cases of hyperkinetic pulmonary hypertension, it has been found that the pulmonary vasculature responds after a time, by producing secondary irreversible changes with intimal thickening and actual luminal occlusion which prevent relaxation of the vascular resistance. This correlates with Edwards' theories on high resistance with a high reserve which later goes on to the irreversible high resistance, low reserve state. The elastic fiber pattern of the pulmonary artery has been noted to be different in congenital and acquired pulmonary hypertension. In fetal life, the elastic fiber pattern in the pulmonary artery and in the aorta is similar. After birth, involution occurs in the pulmonary artery, and the elastic laminae become irregular and develop breaks in their continuity. If, owing to congenital heart disease, the pulmonary artery pressure fails to fall after birth, the pulmonary artery retains its elastic laminar pattern. If hypertrophy occurs as a result of increase in pulmonary artery pressure after involution has taken place, it will develop as thickened, but irregular bands of elastic tissue. Thus, in atrial septal defect, and other forms of acquired pulmonary hypertension, the pulmonary arteries have irregular elastic tissue, while in ventricular septal defect, and other conditions of pulmonary hypertension from birth, the pulmonary arteries resemble the aorta in structure.

With pulmonary hypertension due to organic vascular occlusion, emboli are commonly found, particularly in the lower zones of the lower lobes, and more in the right lung than in the left. Normally, infarction is prevented by collateral flow from the bronchial arteries, but since this is prevented by a rise of pulmonary venous pressure, the danger of infarction is greatest in mitral stenosis where this rise is most prominent. Where the obstruction is due to changes in the arterial walls, the most common example is the intimal proliferation that occurs in small arteries and arterioles in response to severe hypertension. Where the hypertension is due to vascular obstruction by lesions of the lung parenchyma, pulmonary fibrosis in the pneumoconioses is



**FIRST AND FOREMOST FOR FINE
FURNITURE FOR OVER 60 YEARS**

405 Barrington Street,

Halifax, Nova Scotia.

PHONES: 423-8380;

423-8389.

MUTUAL BENEFIT HEALTH & ACCIDENT ASSOCIATION

(Mutual of Omaha)

315 Roy Building

- -

Halifax, Nova Scotia



The Largest Exclusive Health & Accident Company in the World

most common. Other forms of pulmonary fibrosis do not tend to produce pulmonary hypertension. Although emphysema tends to go on to cor pulmonale, it is not believed to do so by vascular obstruction.

SPECIAL CASES

As mentioned before, the obstruction to left ventricular inflow in mitral stenosis has pronounced effects upon the pulmonary circulation. A secondary vasoconstriction compounds the original passive increase in pulmonary artery pressure. With the increase in pulmonary venous pressure, stresses, such as exercise, excitement, fever, and pregnancy, impose an added burden, which may result in pulmonary edema. The common factor in these stress situations is tachycardia, which reduces the ventricular filling time and causes a further elevation in left atrial pressure.

In the case of left to right shunts, the pulmonary blood flow increases, most in atrial septal defect, least in patent ductus arteriosus. When this increase is only moderate, it is accommodated in the distensible pulmonary vessels without a rise in pulmonary artery pressure. Severe pulmonary venous hypertension does not occur unless left ventricular failure is present, and then the levels of pulmonary venous pressure never reach those found in mitral disease. With a torrential pulmonary blood flow, the pulmonary artery pressure rises but with flows greater than three times the normal, this hyperkinetic pulmonary hypertension provokes a further rise in pressure, believed, as we have stated above, to be due to vasoconstriction. The critical point is that the defect must be large enough to increase the blood flow three times the systemic flow, yet with a normal resistance.

In atrial septal defect, if the defect is small, the flow is obviously from left to right because the pressure in the left atrium is greater than that in the right atrium by a few mm. of mercury. If the defect is large, the pressures in the atria are equal,

but the blood passes from left to right by virtue of the greater distensibility of the right ventricle than the left in the presence of equal filling pressures. Progressive dilatation of the right ventricle produces a rise in right atrial pressure and the shunt may reverse, but usually the left atrial pressure increases also and prevents this reversal. This has been attributed to the bulging of the hypertrophied ventricular septum into the left ventricle, obstructing the inflow. The pulmonary hypertension in atrial septal defect is hyperkinetic or vasoconstrictive, but may tend to become obstructive in adult life because of medial hypertrophy, increased hypertension, and superimposed thrombosis.

In ventricular septal defects, the size and not the position of the defect is the more important factor. With defects of greater than 10mm. diameter, the increased blood flow will not be accommodated and hyperkinetic and vasoconstrictive pulmonary hypertension will result. The shunt will be mainly left to right with minimal reversing. Heart failure and respiratory infections are common and the condition is often fatal in infancy. With a defect of 20 mm. in diameter or more, there will result a bi-directional shunt with balanced pulmonary and systemic resistances (see Eisenmenger reaction below). The infundibular hypertrophy, which is part of the right ventricular hypertrophy, may be an important protective mechanism in shielding the pulmonary vascular bed. The pulmonary arterial pressure need not rise progressively in children—the size of the defect relative to the size of the heart may decrease with age, the infundibulum may hypertrophy, the defect may close in systole, or the plane of the septum may act as a baffle—this may be the explanation. However, it is believed that after the age of twenty, pulmonary hypertension begins to increase progressively, especially where the pressure was raised somewhat initially.

Of importance is the development of changes in the pulmonary vessels in subjects with large defects. Normally, the pulmonary vascular resistance falls precipitously at birth; with increased pulmonary flow through a large ventricular septal defect, the pulmonary vasculature does not get a chance to involute, and the vascular capacity becomes fixed. With smaller defects, although the resistance is above normal, the vascular capacity can be increased. Probably with time however, the high resistance, high reserve state associated with small defects goes on to the high resistance, low reserve state as a result of long-standing pulmonary hypertension.

In patent ductus arteriosus, a left to right shunt is the usual case, the amount being proportional to the size of the duct, and inversely related to the pulmonary vascular resistance. If the resistance does not fall at birth, the shunt may be reversed. Progressive pulmonary hypertension is not inevitable, the size of the ductus being important. The hemodynamics are parallel to those in ventricular septal defect, since when the duct is large, the pulmonary blood flow is great, and progressive pulmonary hypertension results because of reactive vasoconstriction followed by medial hypertrophy and intimal changes. The very large duct will be associated with either heart failure early in life, or development of the Eisenmenger reaction and shunt reversal. Coarctation of the aorta in association with a patent ductus does not alter the hemodynamics unless the ductus is inserted distal to the narrowed segment, and the pressure in the aorta in that region is less than in the pulmonary artery, so the blood shunts from the pulmonary artery to the aorta. Pulmonary stenosis may reduce the pulmonary vascular resistance, but since the shunt occurs distal to the obstruction, it does not protect the lungs as it does in ventricular septal defect.

The Eisenmenger syndrome can be defined as severe pulmonary hypertension with balanced systemic and pulmonary vascular resistances, central cyanosis, and a trivial or absent left to right shunt. Originally, the term was used to describe the result of an anatomical anomaly, but has come to be accepted to indicate a hemodynamic anomaly. The reaction or syndrome is three times as common in ventricular septal defect and patent ductus as in atrial septal defect. The genesis is related to whether or not the anatomical defect allows the pulmonary vasculature to involute.

In atrial septal defect, no shunt exists in the neonatal period, and the pulmonary vasculature has the opportunity to involute before it is presented with an increased pulmonary flow. In the small number of cases in which the syndrome does develop, it is related to the hyperkinetic hypertension which must have occurred before complete involution took place. It has been noted that pulmonary stenosis seems never to occur in the Eisenmenger syndrome, and surgically produced pulmonary stenosis has been performed to attempt to allow involution of the pulmonary vascular bed. However, this must be done before irreversible changes have occurred. Most evidence favors the relationship of the syndrome to failure of involution of the pulmonary vascular bed. In some cases, however, a progressive genesis is postulated with this vicious circle:

Excessive flow—hyperkinetic hypertension—reactive vasoconstriction—increased hypertension—medial hypertrophy—further hypertension—further medial hypertrophy—intimal changes—organic occlusive changes in the small arteries—further hypertension—shunt reversal.

Treatment in cases of pulmonary hypertension due to congenital heart defects can be divided into medical and surgical. The use of drugs, such as prisolone, aminophylline, and ganglion blocking agents, has been unsuccessful and disappointing, and is believed to be especially ineffective over the age of five years. Surgery offers help if the defect can be closed while the pulmonary vascular bed is still in its high reserve state. The earlier the operation is performed, and the less the pulmonary hypertension, the lower the operative mortality. But, as the hemodynamics show reversal of shunt and beginning of the Eisenmenger reaction, the more is operation to be contra-indicated. The only hope for the patients with imminent Eisenmenger reaction would be blockage of the shunt early, before secondary changes have fixed the high resistance of the pulmonary vascular bed.

CONCLUSION

One can only conclude that pulmonary hypertension is a clinical entity which must not be overlooked, and although much of our knowledge about it is steeped in uncertainty, a thorough study of it is of great value in understanding cardio-pulmonary physiology and pathology.

BIBLIOGRAPHY

- Bayliss, R.I.S.; Etheridge, M.J.; Hyman, A.L. (1950) *Pulmonary Hypertension in Mitral Stenosis*, *Lancet II*, 889
- Best and Taylor, *Physiological Basis of Medical Practice*, 6th Edition.
- Daley, Goodwin, Steiner, *Clinical Disorders of Pulmonary Circulation*, (1960).
- Edwards, J.E., *Functional Pathology of the Pulmonary Vascular Circulation in Congenital Heart Disease*; *Circulation XV*, 164.
- McIlroy, M.P., Apthorp, G.M. (1958) *Pulmonary Function in Pulmonary Hypertension*, *British Heart Journal XX*, 397.
- Wright, S., *Applied Physiology*, 9th Edition.



NEW...and twice as potent...
NORLUTATE^{*}
(norethindrone acetate, Parke-Davis)

orally active progestational agent for more effective management of amenorrhea... menstrual irregularity... functional uterine bleeding

New NORLUTATE is the acetic acid ester of norethindrone—17-alpha-ethinyl-19-nortestosterone. Physiologically, it is a highly effective oral progestational agent exceeding the known effect of parenterally administered progesterone, oral ethisterone, and norethindrone as well.

The high oral potency of NORLUTATE—approximately twice that of any other progestational agent, milligram for milligram—makes it a drug of choice in many disorders amenable to progestational therapy.

Such therapy can now be instituted to correct endogenous progesterone deficiency more effectively... and without increasing the incidence of side reactions.

Indications for NORLUTATE: Menstrual Disorders—amenorrhea, menstrual irregularity, dysmenorrhea, functional uterine bleeding • Endocrine infertility • Abortion, habitual or threatened • Premenstrual tension • Endometriosis • Pregnancy test.

See medical brochure, available to physicians, for details of administration and dosage.

Packaging: 5-mg. scored tablets, pink, bottles of 30.

^{*}Registered Trademark

53061

PARKE-DAVIS
PARKE, DAVIS & COMPANY, LTD., MONTREAL, Q.

THE MEDICAL SOCIETY OF NOVA SCOTIA

THE NOVA SCOTIA DIVISION of the CANADIAN MEDICAL ASSOCIATION

This Medical Society was founded in 1884 and incorporated in 1861. There are nine Branch Societies in Nova Scotia. It is affiliated with the Canadian Medical Association as the Nova Scotia Division.

The Medical Society of Nova Scotia is a separate body from the Provincial Medical Board which has the authority to grant licenses to practice in Nova Scotia.

Membership in the Medical Society of Nova Scotia and the Canadian Medical Association is voluntary. The total membership in the Medical Society is 637 (1961).

The Organization has 20 Standing Committees and 10 Special Committees; it sponsors 3 research projects and has representatives on 8 organizations.

Members receive a Newsletter at least four times yearly and the Nova Scotia Medical Bulletin each month. Group disability insurance is available to any member regardless of medical history. Eligibility to make application for group life insurance is also a prerequisite of membership.

Membership in the Canadian Medical Association provides the Canadian Medical Journal every two weeks and eligibility to participate in the Canadian Medical Retirement Savings Plan and the Canadian Medical Equity Fund.

Conjoint membership in the Medical Society of Nova Scotia and the Canadian Medical Association is available to any physician licensed to practice in Nova Scotia.

Further information may be obtained from:

C. J. W. BECKWITH, M.D., D.P.H.,
Executive Secretary,
DALHOUSIE PUBLIC HEALTH CLINIC,
UNIVERSITY AVENUE,
HALIFAX, NOVA SCOTIA