Vasodilator Therapy for Pulmonary Hypertensive Disorders

The successful application of vasodilator agents to the treatment of systemic hypertension has stimulated physicians to attempt similar treatment of pulmonary hypertensive disorders. Early reports of success initiated a phase of great optimism. All types of vasodilator drugs have been tried, and newer ones which are close at hand will be tried in the future. Reports of therapeutic failures and unwanted side effects with vasodilator therapy soon swung the therapeutic pendulum toward extreme pessimism. As so often happens in medicine, the swaying is steadied by studies that further define the application of pharmacologic agents to set right the pathologic distortions caused by cardiopulmonary diseases. The via media has not yet been marked out.

The report by Lupi-Herrera and colleagues in this issue (see page 156) is another indication that not all patients with pulmonary hypertension from chronic obstructive pulmonary disease (COPD) are helped by hydralazine, a widely used systemic vasodilator. In their report, hydralazine initially improved arterial and venous oxygen saturations, and decreased systemic vascular resistance, but did not affect pulmonary vascular resistance. Indeed, in one week, even these small benefits were lost. On the other hand, Rubin and Peter reported that in addition to short-term therapy with antibiotics, steroids, oxygen, bronchodilators and chest physiotherapy, some patients, during a stable period with COPD and pulmonary hypertension, respond well to hydralazine, at least during the 48 hours they were monitored. Pulmonary vascular resistance decreased and cardiac output increased both at rest and during exercise. Here, the pulmonary arterial pressures and systemic arterial O2 saturations were higher in the earlier study, but the patients were younger, had higher mixed venous oxygen saturation, and lived near sea level rather than at 2.4 km.

Moreover, the effect of hydralazine on patients with unexplained or primary pulmonary hypertension is incompletely understood. Rubin and Peter found this drug to be effective in reducing pulmonary vascular resistance and improving symptoms, but Packer and co-workers found no beneficial effect in primary pulmonary hypertension or in hypertension secondary to pulmonary embolus, sarcoidosis or interstitial fibrosis. Indeed, many adverse responses were encountered. Some of the differences seem to be accounted for by the studies of Lupi-Herrera and co-workers in patients with primary pulmonary hypertension. In their patients with lower pulmonary arterial pressure, lower pulmonary vascular resistance and pulmonary-to-systemic vascular resistance ratio, hydralazine was helpful. The pulmonary and systemic vascular resistances decreased, cardiac output increased, but pulmonary arterial pressure and the ratio of pulmonary-to-systemic resistance were unchanged. Moreover, in their patients with much higher pulmonary arterial pressures, hydralazine dilated the systemic vascular bed, but did not affect the pulmonary vascular bed or cardiac output. On the other hand, the beneficial effects reported by Rubin and Peter were in patients with pulmonary arterial pressure quite high enough to augur poor results, and at least half the patients studied by Packer and co-workers had pressures that were 45 mm Hg or less.

Which patients are likely to be helped with chronic vasodilator therapy? The elements needed for relief of dyspnea and improved exercise tolerance include pulmonary hypertension induced, in large measure, by active vasoconstriction rather than from irreversible vascular damage or parenchymal fibrosis, adequate ventricular function to propel blood quickly and more efficiently, and a vasodilator drug that induces more pulmonary than systemic vasodilation. Attention must also be directed toward the imprecision of the clinical measurements available to assess these parameters. Prediction of success on the basis of current hemodynamic reckoning is often wide of the mark.

Estimation of the extent to which active vasoconstriction contributes to the increased pulmonary arterial pressure at a given cardiac output is often chancy. The relation of pressure to blood flow, a reflection of vascular resistance, is complex. In the normal lung, the curve is skewed to the pressure axis at the lower flows, and to the flow axis at physiologic or higher flows. Thus, as flow increases, calculated vascular resistance decreases sharply, then more gradually becomes asymptotic. Equally difficult is attempting to learn the effects of a drug on the pressure-flow curve of a diseased lung on the basis of one point on the curve.
before and one during therapy, especially when both parameters are varying. Moreover, pulmonary arterial
data pressure, conventionally expressed in relation to atmosphic pressure, must be adjusted to take into account changes in transpulmonary pressure that are often modified by therapy. Measurement of pulmonary outflow pressure, needed to calculate resistance, is also imprecise. Pulmonary diastolic pressure, wedge pressure and left atrial pressure are not always identical or even close. Their relationships are frequently altered by disease or by subsequent therapy. Calculations should further take into account that in the normal lung left atrial pressure is probably linearly related to pulmonary arterial pressure at very high atrial pressure, and then only if flow is constant. Perhaps the wide variation in response of patients with COPD who have similar pulmonary arterial pressure and vascular resistances suggests that these parameters are less than adequate gauges upon which to base therapy. Moreover, in patients with primary pulmonary hypertension, measurements of pulmonary arterial pressure and resistance may vary spontaneously as much as 22 percent and 36 percent, and may not be the best predictors of survival. The contributions of active vasodilation and of passive changes induced by mechanical variations are not easily sorted out.

The ability of the right ventricle to propel blood through the lung is not always possible to prejude. The right ventricle is afterload-dependent. Although this dependency is related to pulmonary arterial pressure, afterload is more correctly determined by systolic wall stress. Two elements needed to measure wall stress, thickness and ventricular volume, are parameters not readily available in clinical practice. Although afterload, as measured in terms of pulmonary arterial pressure and vascular resistance, does relate inversely to right ventricular ejection fraction, the relationship had a one fourth to one third variance. Pressure and resistance are only part of the complete answer. The dilated hypertrophied ventricle does not work as efficiently as the smaller normal one. Tricuspid insufficiency also alters afterload to important proportions. Although frequently undetected at the bedside, it may well account for reports of normal right ventricular ejection fraction in patients with very high pulmonary arterial pressure and resistance. Further, right ventricular contractility is affected by coronary artery disease. Although the significance of interaction of left and right ventricular contraction remains unclear, posteroinferior left ventricular infarction frequently impairs right ventricular function, and stenosis of the right coronary artery may further decrease function in arteriosclerotic coronary disease. Adverse or poor vasodilator responses in older pulmonary hypertensive patients may relate, in some measure, to unsuspected coronary artery disease, especially with hypoxemia, and impaired left ventricular function.

Medical literature abounds with evidence that most systemic vasodilator drugs will also dilate the pulmonary vascular tone. No methods are at hand to reliably predict the relative dilator effects on the systemic and pulmonary beds. Moreover, the effects of these drugs on pulmonary hypertensive states induced passively by mechanical factors or pulmonary venous hypertension is small or insignificant. Unfortunately, marked systemic vasodilation without equal or greater pulmonary vasodilation causes systemic hypotension; obstruction in the pulmonary vascular bed impairs the heart's ability to increase blood flow enough to sustain systemic blood pressure. Recognizing the limited clinical ability to differentiate active from passively induced pulmonary hypertension, and to accurately predict right ventricular contractility, physicians must anticipate untoward responses such as decreased systemic blood pressure and cardiac output without significant improvement in pulmonary artery pressure. More importantly, searches for better drugs that have predominantly pulmonary vasodilator activity, or that are metabolized in a single pass through the pulmonary vascular bed, have not yet been fruitful. The response to these drugs must be monitored over long periods, since hemodynamic efficacy does not of itself establish therapeutic value in terms of relief of symptoms or improved longevity. Prostaglandin £, a systemic and pulmonary vasodilator which is metabolized and largely inactivated in the lung, seems to have been helpful on a short-term basis. However, PGE is administered parenterally, and the dose used might have exceeded the metabolic capability of lungs with severe parenchymal disease and diminished endothelial surface area. At the start, the response to nifedipine has been inconsistent, but few observations are yet available. A combination of drugs may be helpful, but not all drugs that are effective in systemic hypertension will be useful. Beta adrenergic blocking drugs such as propranolol, which are widely used in treating systemic hypertension, may well be avoided, since beta adrenergic blockade enhances pulmonary vasoconstrictor responses to norepinephrine and epinephrine.

Nonetheless, the pendulum still lingers in the pessimistic segment. The hemodynamic responses found so far in responsive patients with either primary pulmonary hypertension or stable COPD have been less than dramatic. Even these responses, measured for the most part over short periods, have not yet established the therapeutic value in terms of patient wellbeing or longevity. On the other hand, most patients selected for treatment are far along in the natural course of the disease with advanced vascular and parenchymal pathology. To treat the disease successfully, stumbling blocks must be removed.
Pulmonary hypertension should be recognized early, passive factors must be cleaved away from the active vasoconstrictor contribution to hypertension, right ventricular systolic wall stress measured, and more specific vasodilators developed. The nature of pulmonary endothelial metabolism and the mechanism of vascular smooth muscle contraction must be brought to light. In spite of divergent therapeutic responses of patients with these protein diseases, further carefully controlled long-term studies with good hemodynamic monitoring should not be discouraged.

As the target clears and our therapeutic devices are honed, divergence will diminish and vasodilator therapy should become more effective.

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Estimation of the Energy Expenditure During Work

Assessment of the ability of a worker with cardio-pulmonary impairment to perform his job is a difficult task. One approach is to compare the worker’s remaining functional capacity with the demands of his job to estimate the physiologic “stress” during work. Exercise requiring a minute ventilation greater than 50 percent of the measured maximal voluntary ventilation at rest is likely to be associated with dyspnea. Sustained exercise at levels above 35 percent of the maximal aerobic power (\(\dot{V}O_2\)max) produce excessive fatigue. Estimation of the expenditure of energy during work can be done by direct collection of expired air to measure oxygen consumption (\(\dot{V}O_2\)) or by measuring only heart rate during work and making use of the essentially linear relationship between heart rate and \(\dot{V}O_2\). This relationship varies depending, among other things, on sex, body size, and state of physical fitness, but can be determined for individuals by submaximal exercise testing in the laboratory. This latter approach was used by Harber and co-workers (see page 226) to estimate the energy expenditure of 12 underground coal miners in several job categories.

While providing estimates for the relative energy expenditure requirements of modern mining jobs, the results point out some of the inherent difficulties in using these estimates to assess the ability of an individual to perform a given job. Although given only in units relative to resting (METS), the expenditure of energy clearly varied importantly between workers with the same job title. Younger workers appeared to spend more time at higher levels of exertion than older workers with the same job. If workers can choose the pace or timing of periods of varying levels of work intensity, older workers may be able to accomplish the same total amount of exertional work as younger workers, without excessive stress despite lesser physiologic capacity. Also, subjects with severe cardio-