Evaluation of the Circulation—Pulmonary and Otherwise—in Man

MANY GROUPS have studied the effects of anesthetic agents on the systemic circulation in man. Few have examined the equally important topic of the effects of anesthesia on regional circulations. Among these few have been investigators at the University of Pennsylvania. In this issue of ANESTHESIOLOGY [1] they have extended their work to include what is perhaps the most important of the "regional" circulations: the pulmonary circulation.

The pulmonary circulation is no ordinary regional circulation, for almost the entire output of the heart must pass through it. Therefore, any pharmacologic agent which influences the pulmonary circulation may secondarily influence the systemic circulation, and *vice versa.* Another important feature of the pulmonary circulation is that during the early stages of induction the distal half is at any instant exposed to the highest concentration of an inhalation anesthetic.

If the pulmonary circulation is important, why have anesthesiologists devoted considerable energy to the systemic circulation and so little time to the pulmonary circulation? * The reason for the paucity of studies lies in the fact that this circulation is difficult to investigate. At first glance it would seem that the pulmonary circulation would be one of the most directly accessible of the regional circulations; certainly the proximal part is relatively easy to reach in man. Right ventricular or pulmonary artery catheterization is a more acceptable investigative technique than hepatic, carotid, or renal artery catheterization. However, the distal part of the circulation—the left atrium and pulmonary veins—is almost impossible to reach. Yet pressure measurements at one of these sites are needed to calculate pulmonary vascular resistance.

The resistance to flow in a tube depends upon viscosity and geometry, and rises if the fluid is thicker, the tube narrower, or the distance between the points longer. As shown by the relationship first discovered by Poiseuille, the tube radius is the major determinant of resistance: $R = P/Q = 8l\eta/\pi r^4$, where R = resistance, P = pressure, Q = flow, l = length, η = viscosity, and r = radius. To calculate pulmonary vascular resistance, then, we need to know the flow through the lungs and the mean pressure drop from pulmonary artery to pulmonary veins. Flow can be measured by the Fick principle or with indicator dilution curves, and while they probably give reasonable approximations to the actual flow, both methods have drawbacks.[3-5] Since it is difficult or impossible to pass a catheter into the pulmonary veins, their pressure is measured indirectly by the "wedge" technique. A catheter with a single end opening is advanced as far distally as possible in a pulmonary artery. These arteries are end arteries; thus, their complete occlusion by the catheter allows no more blood to enter that segment. Therefore, pressure in the vessel falls until it equilibrates with the pressure in the vessels distal to the capillary bed, that is, the pulmonary veins. Proper wedging of the catheter is not always easy to verify.[6] The best proof is to withdraw blood through the catheter and show that, unlike pulmonary arterial blood, it is nearly fully saturated. If, however, pulmonary vascular resistance is high, it may not be possible to withdraw a sample. Demonstration of pulmonary venous pressure waves, which pass retrograde from pulmonary vein to catheter, is possible, but they may not always be seen if resistance is high, and they can be artifactually simulated if the catheter is only partly wedged. When in doubt, cautious angiography can confirm wedging.[6]

Pulmonary venous and left atrial pressures are usually the same, but can differ if there is stenosis of the vein, cor triatriatum, or physiologic constriction of small pulmonary veins.[7, 8]

* Aviado [2] in a thorough 1,200-page review of the pulmonary circulation, was able to gather only 13 references on the effects of inhalation anesthetic agents on the pulmonary circulation. In contrast, there are more than 350 articles on the effects of halothane or methoxyflurane on the systemic circulation.

The assumption of equality may need to be defended in any particular experiment, particularly if the wedge pressure is used to evaluate myocardial function.

If we have measured pulmonary venous pressure adequately, calculation of pulmonary vascular resistance is easy, but its interpretation is not. In vascular beds, factors other than those listed above affect resistance: branching, change of direction, and variation in diameter of tubes from one segment to another all cause greater pressure drops than would be expected from the Poiseuille equation. In any one person it is customary to assume that these factors and the lengths of the vessels are approximately constant. We, therefore, attempt to interpret changes in resistance to give information about constriction and dilation of small vessels. However, blood viscosity is not constant, but varies with shear rate [9] so that it has different values in vessels of different diameters and at different cardiac outputs. Furthermore, vessel diameter can widen when pulmonary arterial flow and pressure increase,[10] or narrow when they fall. It is fortunate, therefore, that in the studies reported by Price *et al.* cardiac output changed very little. The pulmonary vessels can dilate passively when left atrial pressure is raised acutely [11, 12]: all other things being equal, a pressure drop from pulmonary artery to left atrium of 25 to 14 mm Hg should be associated with a lower resistance to flow than is a drop of from 15 to 4 mm Hg. Lung inflation can raise resistance.[13] Innumerable chemical agents can change resistance. Hypoxia (an oxygen tension of below 60 in the alveoli) [14] and acidemia (below a *p*H of 7.2) [14] are potent vasoconstrictors, especially together, while carbon dioxide appears to be a mild pulmonary-artery vasodilator.[15] Bradykinin and alpha-receptor blocking agents are pulmonary vasodilators, while catecholamines in general cause vasoconstriction. Therefore, any procedure which might stimulate the production of these substances could have effects on resistance which would be falsely attributed to the procedure itself.

Failure of an agent or procedure to cause any or only a slight change in pulmonary vascular resistance in normal adults cannot be extrapolated to patients with thickened media of the small pulmonary arteries. Thus, infants, inhabitants of high altitude, and patients with cor pulmonale or large ventricular septal defects could all respond differently to the same stimulus and need separate investigation.

Finally, there is evidence that flows through different portions of the lung are unequal,[16] especially in the erect position. Therefore, the calculated resistance figure is an average, which can hide shifts of resistance from one region to another. It is possible, for example, for resistance to rise at the lung bases in mitral stenosis so that flow is diverted to low-resistance vessels higher up, the total calculated resistance being normal.

Since the systemic and pulmonary circulations are interdependent, we must also discuss the data gathered on the systemic circulation. The authors of the paper in this issue wished to compare measurements taken during the conscious state with those taken under anesthesia during spontaneous ventilation. Since the agents tested depress ventilation, a rise in Pa_{CO_2} and drop in *p*H were inevitable. They then chose to maintain this respiratory depression during controlled ventilation, that is, maintain the same Pa_{CO_2} and *p*H by controlled hypoventilation. Thus, the blood gas values during anesthesia were different from those during the awake state. Although the changes in Pa_{CO_2} seen in this study have little effect on pulmonary vasculature, they do have a significant effect on the systemic circulation. Carbon dioxide itself is a vasodilator and myocardial depressant. It can release epinephrine and norepinephrine,[17] which antagonize these effects. The result of a moderate increase in Pa_{CO_2} is, under most circumstances, myocardial stimulation plus overall vascular dilation.[18] These effects can counteract the depressant effects of halothane. Thus, while most investigators have observed a decrease in cardiac output under halothane–oxygen anesthesia,[19] Price *et al.* observed none. Other measurements in the systemic circulation might be expected to have been affected by this change in Pa_{CO_2}. One way to escape this dilemma and still retain the original protocol would have been to add CO_2 to the inspired gas mixture during the conscious control state—trying to predict the ultimate Pa_{CO_2} during anesthesia in a given

subject. This, of course, would have been difficult.

The changes in the systemic circulation produced by an increase in oxygen tension—an increase in systemic peripheral resistance and a decrease in cardiac output—were not obtunded by halothane during spontaneous ventilation. They were, however, obtunded during controlled ventilation. Other studies have confirmed this absence of change in the systemic circulation when halothane–oxygen is changed to halothane–air during controlled ventilation.[20] This leads to an interesting question: how much of the circulatory response to a change in oxygen tension is due to factors other than the changed oxygen tension? In the study of Price *et al.*, *p*H and Pa_{CO_2} remained stable when oxygen tension was changed, so these could not have influenced the circulation. Volunteer subjects can be trained to accept controlled ventilation while conscious. It would be interesting to measure the circulatory response to changes of oxygen tension in the conscious state during controlled ventilation.

Evaluation of myocardial function in man remains difficult. The authors have approached it by a time-honored method—the ventricular-function curve. The Frank–Starling Law states that the greater the initial ventricular fiber length, the greater the strength of contraction. This is convenient for the heart, which is working against constantly varying loads and inputs, but is very inconvenient for the investigator. He must worry about whether a change in ventricular function is due to a change in "contractility" or to a change in some extrinsic factor, such as end-diastolic filling. The ventricular-function curves, which plot a variable reflecting the initial fiber length against a variable reflecting function—in other words, a Starling curve—can solve part of this problem. The authors chose for the latter variable stroke work, which, while useful, has drawbacks. A pertinent editorial by Blinks [21] comments on the Starling ventricular-function curves in general and the use of stroke work in particular.

The use of pulmonary wedge pressure as an indicator of end-diastolic pressure or volume, the former variable, is yet another matter. In the first place, the mean wedge pressure is not the same as the left ventricular end-diastolic pressure, which occurs at a single point in the cycle. Even if "a" waves are seen in the wedged tracing, it is difficult to relate these to a specific end-diastolic pressure. If the PR interval changes, then the influence of atrial contraction on the end-diastolic pressure will vary. Furthermore, even if left ventricular end-diastolic pressure is obtained, it is not easy to relate it to fiber length. As many workers have demonstrated,[22] left ventricular volume or fiber length can change greatly with little change of pressure. And many anesthetic agents, particularly cyclopropane,[23] influence ventricular compliance.* Thus, a change in end-diastolic pressure may not reflect a proportional change in end-diastolic volume, or in initial fiber length. This is what the ventricle sees when it begins to contract—the initial fiber length.

It is hoped that our comments will not be construed as a criticism of the investigations reported by Price *et al.*, but rather as an extension of interpretation of their results and a suggestion for further investigations. The authors have made a significant contribution by performing experiments in man. This is where the ultimate interests of all of us in medicine lie. Any experiments in man require care and ingenuity, and the authors have used both. They have performed long-needed studies on the pulmonary circulation, and have extracted as much information as is possible with present methods. Their controls were well conceived. They have demonstrated that the striking difference between halothane and cyclopropane, which has manifested itself in so many aspects of the circulation, also exists in their effects on the pulmonary circulation.

This work, like many other works by this group, will serve as the foundation on which many other investigations will be based.

N. Ty Smith, M.D.
Assistant Professor of Anesthesia
Department of Anesthesia
Stanford University School of Medicine
Stanford, California

Julien I. E. Hoffman
Associate Professor of Pediatrics
University of California Medical Center
Cardiovascular Research Institute
San Francisco, California

* The term "compliance" is used as the respiratory physiologist defines it.

References

1. Price, H. L., Cooperman, L. H., Warden, J. C., Morris, J. J., and Smith, T. C.: Pulmonary hemodynamics during general anesthesia in man, ANESTHESIOLOGY **30**: 629, 1969.
2. Aviado, D. M.: The Lung Circulation. Volume 2. New York, Pergamon Press, 1965, pp. 670–706.
3. Wood, E. H., Bowers, D., and Shepherd, J. T.: Cyclic variations in oxygen content of central venous blood in man, Amer. J. Physiol. **179**: 685, 1954.
4. Jacobs, R. R., Schmitz, U., Heyden, W. C., Roding, B., and Schenk, W. G., Jr.: A comparison of the accuracies of the electromagnetic flowmeter and the cardio-green dye dilution blood flow measurement techniques in a model, Surg. Forum **19**: 113, 1968.
5. Sleeper, J. C., Thompson, H. K., McIntosh, H. D., and Elston, R. C.: Reproducibility of results obtained with indicator-dilution technique for estimating cardiac output in man, Circ. Res. **11**: 712, 1962.
6. Bell, A. L., Jr., Haynes, W. F., Jr., Shimomura, S., and Dallas, D. P.: Influence of catheter tip position on pulmonary wedge pressures, Circ. Res. **10**: 215, 1962.
7. Aviado, D. M.: Pulmonary venular responses to anoxia, 5-hydroxytryptamine and histamine, Amer. J. Physiol. **108**: 1032, 1960.
8. Eliakim, M., Rosenberg, S. Z., and Braun, K.: Effect of hypertonic saline on the pulmonary and systemic pressures, Circ. Res. **6**: 357, 1958.
9. Burton, A. C.: Physiology and Biophysics of the Circulation. Chicago, Year Book Medical Publishers, Inc., 1965.
10. McGregor, M.: Pulmonary hypertension. *In* Cander, L., and Moyer, J. H. (eds.): Tenth Hahneman Symposium on Aging of the Lung—Perspectives. New York, Grune and Stratton, 1964.
11. Borst, H. G., McGregor, M., Whittenberger, J. L., and Berglund, E.: Influence of pulmonary arterial and left atrial pressures on pulmonary vascular resistance, Circ Res. **4**: 393, 1956.
12. Rudolph, A. M., and Auld, P. A. M.: Physical factors affecting normal and serotonin-constricted pulmonary vessels, Amer. J. Physiol. **198**: 864, 1960.
13. Simmons, D. H., Linde, L. M., Miller, J. H., and O'Reilly, R. J.: Relation between lung volume and pulmonary vascular resistance, Circ. Res. **9**: 465, 1961.
14. Rudolph, A. M., and Yuan, S.: Response of the pulmonary vasculature to hypoxia and H^+ ion concentration changes, J. Clin. Invest. **45**: 399, 1966.
15. Viles, P. H., and Shepherd, J. T.: Evidence for a dilator action of carbon dioxide on the pulmonary vessels of the cat, Circ. Res. **22**: 325, 1968.
16. West, J. B.: Topographical distribution of blood flow in the lung. *In* Handbook of Physiology. Section 3, Respiration, Vol. 2, pp. 1437–1451, Published for the American Physiological Society, Washington, D. C., 1965.
17. Sechzer, P. H., Egbert, L. D., Linde, H., Cooper, D. Y., Dripps, R. D., and Price, H. L.: Effect of CO_2 inhalation on arterial pressure, ECG, and plasma catecholamines and 17-OH corticosteroids in normal man, J. Appl. Physiol. **15**: 454, 1960.
18. Dripps, R. D., and Comroe, J. H., Jr.: The respiratory and circulatory response of normal man to inhalation of 7.6 and 10.4 per cent CO_2, with a comparison of the maximal ventilation produced by severe muscular exercise, inhalation of CO_2 and maximal voluntary hyperventilation, Amer. J. Physiol. **149**: 277, 1947.
19. Price, H. L.: Circulation during Anesthesia and Operation. Springfield, Ill., Charles C Thomas, 1967, pp. 33–34.
20. Smith, N. T., Eger, E. I., II, Stoelting, R. K., Whitcher, C. E., and Whayne, T. F.: The circulatory effects of the addition of nitrous oxide to halothane anesthesia in man, ANESTHESIOLOGY **29**: 212, 1968.
21. Blinks, J. R.: On the measurement of myocardial contractility (editorial), ANESTHESIOLOGY **28**: 800, 1967.
22. Braunwald, E., and Ross, J., Jr.: The ventricular end diastolic pressure (editorial), Amer. J. Med. **34**: 147, 1963.
23. Hamilton, W. K., Larson, C. P., Bristow, J. D., and Rapaport, E.: Effect of cyclopropane and halothane on ventricular mechanics: A change in ventricular diastolic pressure volume relationship, J. Pharmacol. Exp. Ther. **154**: 566, 1966.