



MONITOREO HEMODINÁMICO

Occasional Essays A Century of Pulmonary Hemodynamics

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At the start of the twentieth century, studies of pulmonary hemodynamics were largely confined to measurements of pulmonary arterial pressures in anesthetized, open-chest animals undergoing artificial respiration (1). By then, pressure recording was fairly well standardized, and pressures recorded in animals by different manometric systems were generally accurate and similar in form (2). Outflow pressures, for the calculation of pulmonary vascular resistance and the measurement of left arterial measures, became available at midcentury (3). A leading figure in setting standards for pressure recording was Otto Frank (1865–1944), a distinguished German physiologist and physician, whose name is well known to circulatory physiologists as one of the discoverers of the Frank-Starling law of the heart. Less familiar, but seminal for the study of hemodynamics, was his role in setting standards for the accurate recording of vascular pressure pulses (4). These standards featured prominently in the subsequent design and application of cardiac catheters for human use.

Another iconic physiologist of that time was Ernest Henry Starling (1866–1927) whose heart–lung preparations that made it possible for experimental observations to be made under rigorously controlled conditions so that physiologic factors and mechanisms could be isolated and analyzed in mechanical and physiologic terms. From such preparations were derived the Frank-Starling law of the heart and Starling's forces involved in capillary exchange. However, observations made under such artificially controlled conditions paid the penalty of obscuring automatic adjustments that occur under more natural conditions (Figure 1).

The modern era of measuring pulmonary blood flow began in 1912 with August Krogh and Johannes Lindhard who used nitrous oxide as the test gas and popularized the use of gas uptake methods in humans (5). The use of indirect methods became widespread. However, the indirect methods were handicapped by two major uncertainties: (1) early recirculation, which artificially decreased the value for cardiac output by diminishing the uptake of gas from the alveoli, and (2) the use of alveolar gas sampling to estimate the content of the regulatory gases in blood returning to the heart (6).

A direct approach to measuring cardiac output was suggested by Adolph Fick in 1870 in a short commentary to his local medical society in Würzburg, Germany (Figure 2) (7). He indicated that the cardiac output could be measured by

dividing the oxygen uptake by the corresponding arteriovenous difference in oxygen content. Carbon dioxide could serve equally well as the test gas. However, not until two decades later did physiologists begin to apply the Fick principle in animals (2).

At the start, application of the Fick principle in humans was handicapped primarily by the difficulty in obtaining samples of mixed venous blood. Sporadic attempts to obtain blood samples were made by such formidable interventions as transthoracic needling of the right ventricle and the passage of a tube into the right atrium via a large neck vein. More often, indirect measures were applied. For example, Loewy and von Schrötter, using a bronchoscopic technique, used samples of alveolar air that had been equilibrated with mixed venous blood by inflating a balloon in a proximal bronchus.

With the passage of time, it became clear that valid application of the Fick principle in humans was more complicated than originally envisaged. Three guidelines in particular had to be observed: (1) a steady state of the respiration and circulation had to be achieved, (2) blood and alveolar air had to be sampled simultaneously, and (3) the test gas (i.e., O₂ or CO₂) had to be measured in mixed venous blood rather than in peripheral venous blood (8). A novel way to satisfy the last requirement was demonstrated by Werner Forssmann of Eberswalde, Germany (Figure 3). Forssmann, in heroic experiments on himself, showed that the right side of the heart could be safely



catheterized by way of a peripheral vein (9). His interest was in cardiac injections rather than in blood sampling from within the heart. To convince others about the safety of the procedure, he catheterized himself on several different occasions and walked about, with catheter in place, climbing the stairs en route to the X-ray department. Forssmann made sure that others were aware of his accomplishment and its prospects. However, instead of earning plaudits for his pioneering effort, Forssmann was rewarded with criticism and ridicule by his colleagues and by administrators.

Forssmann's demonstration attracted more attention in Europe and South America than in Germany. In the United States, the lead was taken in the 1940s by the Cardiopulmonary Laboratory at Bellevue Hospital in New York City (Figure 4) (10). André F. Cournand was the director of the laboratory, which was sponsored by both the Chest Service run by J. Burns Amberson, M.D., and the Medical Division of Columbia University, headed by Dickinson W. Richards, M.D. With the strong support of these two sponsors, André Cournand established a world-renowned cardiopulmonary laboratory. In 1951, I rotated through the laboratory as an Established Investigator of the American Heart Association and subsequently rejoined it as a member of the research team on the faculty of the College of Physicians and Surgeons of Columbia University.

Spurred on in large part by the Bellevue laboratory, the use of cardiac catheterization for diagnostic purposes spread quickly throughout medical centers in the United States and abroad. In 1956, Forssmann shared the Nobel Prize with Cournand and Richards for their respective roles in introducing and standardizing cardiac catheterization. As usage spread, modifications in equipment and technique made it possible to move cardiac catheterization from the fluoroscopy room to the bedside where hemodynamic monitoring could be substituted for radiographic visualization of the catheter tip. In 1953, Michael Lategola and Hermann Rahn showed in animals how to obtain a measure of outflow pressures for the determination of pulmonary vascular resistance. They used a flow-directed catheter with an inflatable balloon at its tip to measure left atrial pressure (11). In 1950, Hellems and colleagues modified the technique to measure pulmonary "capillary" pressure in humans (12). The next step was to move the technique from the fluoroscopy suite to the bedside. In 1970, William Ganz and Harold J. C. Swan introduced a multilumen, balloon-tipped catheter that could be advanced and the tip positioned under hemodynamic monitoring. Once in place, the multilumen catheter made it possible to record simultaneously the pressures in the pulmonary artery and left atrium (13). Control of the pulmonary circulation was first studied in open-chest, anesthetized animals. Although these studies showed that stimulation of nerves to the lungs could affect pulmonary hemodynamics, there was consensus in the 1940s that the pulmonary nerves played little, if any, role in regulating the normal pulmonary circulation. In 1946, attention shifted from nerves to local self-regulatory mechanisms. The shift was prompted by the demonstration of von Euler and Liljestrand, in anesthetized cats, that acute hypoxia elicits pulmonary vasoconstriction (Figure 5) (14, 15). Shortly thereafter, the experiments with acute hypoxia in anesthetized cats were repeated in normal, awake humans. Thus, in 1947, Motley and colleagues, in the Cournand-Richards Laboratory, exposed five human subjects to 10% oxygen in nitrogen for 10 minutes and observed an increase in pulmonary arterial pressure and in pulmonary vascular resistance, which indicated that acute hypoxia had elicited pulmonary

vasoconstriction (10, 16). These observations on hypoxic pulmonary vasoconstriction raised the possibility of an intrinsic self-regulatory mechanism within the lungs that would automatically direct incoming mixed venous blood to well-aerated alveoli, thereby optimizing external gas exchange.

Included in the results of Motley's experiments was the puzzling conclusion that the increase in pulmonary arterial pressure induced by acute hypoxia was accompanied by a decrease in cardiac output. Subsequent investigation showed that this unanticipated outcome was an artifact due to failure to allow sufficient time during hypoxia for a new steady state of the respiration and circulation to be established (8). Clarification of this issue played a key role in establishing guidelines for the valid application of the Fick principle.

While Cournand and Richards were exploring the pulmonary circulation in adult humans, Geoffrey S. Dawes, C.B.E., was doing the same for the pulmonary circulation of the fetus (Figure 6). Dawes had been trained in physiology and pharmacology at several of the foremost laboratories in the United States but spent virtually all of his subsequent research career as Director of the Nuffield Institute for Medical Research in Oxford, England. Using the pregnant ewe as the experimental animal, he pursued this line of research in the footsteps of Sir Joseph Barcroft of Cambridge, England, whose research had been interrupted by the outbreak of the First World War. Although his research was done on animals, it was directly related to human applications (17).



Figure 6. Geoffrey Sharman Dawes (1918–1996). Dawes spent virtually all of his career as Director of the Nuffield Institute for Medical Research. He carried on in the tradition of Sir Joseph Barcroft who had pioneered research in fetal physiology using animal experiments to gain insights that were directly transferable to the human fetus and newborn.

PULMONARY HEMODYNAMICS IN PRIMARY PULMONARY HYPERTENSION

Considerable insight into pulmonary hemodynamics has been provided by physiologic studies on primary pulmonary hypertension. The physiologic studies were preceded by histopathologic observations made in individuals who died of primary pulmonary hypertension (18, 19). The first clinical–pathologic case report was made in 1891 by Ernst von Romberg, a distinguished German physician and clinical scientist. Unable to uncover any cause for the abnormalities in the pulmonary blood vessels, he designated the intrinsic pulmonary vascular disease as "pulmonary vascular sclerosis" (19). This case report led to similar case reports by others, along with speculation and debate about the etiology of the disease. In 1901, in an unpublished lecture in Buenos Aires, Abel Ayerza coined the descriptive term "cardiacos negros" to describe a syndrome that today would be categorized as pulmonary hypertension and right ventricle failure. His colleagues in Argentina designated the syndrome "Ayerza's disease" and proposed syphilis as its etiology. Between 1901 and 1925, case reports from South and North America and Europe supported the view that the pulmonary vascular sclerosis described by Romberg was due to syphilitic pulmonary arteritis. Despite some misgivings about the syphilitic etiology of primary pulmonary hypertension, the belief remained popular until the 1940s.

The widespread belief in syphilis as the cause of primary pulmonary hypertension was finally laid to rest in the 1940s by Oscar Brenner, M.D., of Birmingham, England (20). While a Rockefeller Traveling Fellow, he reviewed 100 case reports of pulmonary hypertension in the autopsy files of the Massachusetts General Hospital. Twenty five of these patients carried the diagnosis of Ayerza's disease. Based largely on this personal review and his review of the literature, Brenner concluded that Ayerza's disease was neither a clinical nor a pathological entity and that syphilis was not the cause of the disease. He pinpointed the small muscular arteries and arterioles as the seat of the pulmonary hypertension and described their histopathologic features. Brenner was a histopathologist rather than a physiologist (20). As a result, he did not recognize the role played by vasoconstriction in the pathogenesis of primary pulmonary hypertension, nor did he appreciate the causal relationship between the pulmonary vascular lesions and the dilated, hypertrophied right ventricle, which he pictured as separate consequences of a shared insult.

Clinical interest in pulmonary hypertension was heightened considerably by the teaching and writings of Paul Wood, a superb British cardiologist, teacher, and showman. In the 1950s, he played a pivotal role in bringing the pathophysiology of congenital and acquired heart disease to the bedside and in determining operability. His 1950 textbook, *Diseases of the Heart and Circulation*, still stands as a landmark in the cardiovascular literature (21).

A breakthrough in uncovering the pathophysiology of primary pulmonary hypertension began in 1951 with the demonstration by Dresdale and coworkers

that pulmonary vasoconstriction is involved in the pathogenesis of primary pulmonary hypertension (22). They elicited a dramatic decrease in pulmonary arterial pressure in a patient with primary pulmonary hypertension by infusing the systemic vasodilator tolazoline (priscoline) intravenously. However, this seminal observation was not conclusive because of the possibility, raised by studies of Starling on the heart–lung preparation, that the decrease in pulmonary arterial pressure could be secondary to systemic vasodilation caused by the drug. This uncertainty was dispelled few years later by Harris and by Wood, who substituted acetylcholine for tolazoline, thereby taking advantage of the fact that acetylcholine injected intravenously is eliminated from the blood during its passage through the pulmonary circulation (23).

THE AMINOREX EPIDEMIC

Interest in so-called primary pulmonary hypertension was excited in 1967–1972 by an epidemic of pulmonary hypertension attributed to the ingestion of an appetite suppressant, aminorex fumarate (24). In patients who came to autopsy, the pulmonary vascular lesions caused by the drug were identical with those of primary pulmonary hypertension. Since then, similar lesions have been found in other pulmonary hypertensive diseases, such as that caused by human immunodeficiency virus infection. Not only did the aminorex epidemic demonstrate that relatively few who took the drug developed pulmonary hypertension, but the relatively small number of individuals who developed the



disease also suggested that inherited susceptibility may play a role in the pathogenesis of the disease.

Stimulated largely by the aminorex epidemic, a meeting of the World Health Organization was convened in 1975 to gather and review the scattered clinical and physiologic data about primary pulmonary hypertension. The report of this meeting identified shortcomings in the understanding not only of primary pulmonary hypertension but also of normal pulmonary hemodynamics. In addition, it recommended that ambiguities in nomenclature be eliminated. Finally, the report called for a worldwide registry that would gather data about the prevalence and natural history of primary pulmonary hypertension, which was regarded as a rare disease.

AFTER THE WORLD HEALTH REPORT

The recommendation concerning a registry was implemented in 1981. This registry, which consisted of 32 clinical centers geographically distributed throughout the United States, a Coordinating Core, and a Pathology Core, collected data for 6 years. By the time the registry closed in 1987, clinical, physiologic, and therapeutic data had been collected in standardized fashion on more than 200 patients with primary pulmonary hypertension. The registry had several favorable outcomes: (1) it sharpened clinical and pathologic diagnostic criteria, (2) provided a standardized format for data collection, (3) led to the exploration and systematic evaluation of pulmonary vasodilators, (4) promoted subsequent cooperative studies among the investigators at various centers, and (5) promoted public awareness of the disease.

A second meeting of the World Health Organization was held in Evian, France, in 1998. Instead of confining itself to primary pulmonary hypertension, the Evian meeting created a clinical classification of all pulmonary hypertensive diseases that is oriented toward the prevention and treatment of pulmonary hypertensive diseases. The effectiveness of the Evian diagnostic clarification was evaluated at the third meeting of the World Health Organization in Venice, Italy, in 2003. Consensus was reached that the classification has proved to be valuable for clinical and epidemiologic purposes but less so for research. This reservation was not unexpected because the classification focuses on diagnosis and treatment, whereas research on primary pulmonary hypertension has become increasingly reductionistic in nature.