A History of the Diagnosis and Treatment of Venous Thrombosis and Pulmonary Embolism

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The history of venous thrombosis and pulmonary embolism echoes the naes of Harvey, Virchow, Margagni, Lannec, Trendelenberg, Ochsner DeBakey, Murray and many other famous figures in medicine. Through anatomical observation, physiologic experimentation, and laboratory or clinical investigation, they individually and collectively contributed to our current knowledge and approach to the treatment of these common and often life-threatening maladies. This article chronicles the important historical milestones in the understanding and development of current surgical and medical management of thromboembolic disease.

McFadden PM, Ochsner JL. A history of the diagnosis and treatment of venous thrombosis and pulmonary embolism. The Ochsner Journal 2002; 4:9-13.

Nothing is more tragic than a sudden, instantaneous fatality from a massive pulmonary embolus following an apparently normal convalescence from an uncomplicated medical illness or routine surgical procedure. Of the approximately 650,000 people afflicted with pulmonary thromboembolic disease in the United States each year, more than 200,000 die from pulmonary embolism (1). This estimate is probably low since many incidents go undiagnosed. Pulmonary embolism is the most common pulmonary disorder found at autopsy in hospitalized patients and the most lethal pulmonary condition in the United States (2-4).

Despite landmark anatomical observations by William Harvey in the early 1600s, which confirmed the direction of blood flow through the circulation, the concept of pulmonary infarction and ultimately venous thromboembolism took another 200 years to eventually surface. Early in the 18th Century, Giovanni Batista Morgagni asked "Where is the disease?" when he had no explanation for the presence of large clots in the pulmonary arteries found at autopsy in patients who had died suddenly. In a treatise on diseases of the heart and lung, Laennec in 1819 first described the pathologic features of hemorrhagic pulmonary infarction and differentiated it from other causes of hemoptysis (5). Jean Cruveilhier, a contemporary of Laennec and celebrated French pathologist, in his book entitled "Anatomie Pathologique du Corps Humain" hypothesized that the cause of all disease was phlebitis. He reached this conclusion by noting blood clots in corpses he had autopsied. In this treatise, Cruveilhier further detailed the pathologic anatomy of "pulmonary apoplexy" previously described by Laennec by adding "…all arterial branches which lead to those lesions were filled with clots that branched according to the vascular tree" (6). Neither Laennec nor Cruveilhier considered the origin of pulmonary emboli to be veins of the lower extremities or pelvis since both men regarded the thrombi to be arising primarily in the pulmonary arteries (7).

It was Rudolph Virchow, a century and a half ago, who defined the pathophysiology of pulmonary embolism while investigating Cruveilhier's doctrine. Virchow realized that a venous thrombus can break loose from its origin, travel through the blood stream, and involve the vessels of other organs. More specifically, he emphasized the embolic potential of thrombi propagating into the vena cava: "…a plug may extend into the vena cava as thick as the last phalanx of the thumb. These are the thrombi that constitute the source of real danger; it is in

them that ensues the crumbling away which leads to secondary occlusion in remote vessels" (8). He observed two types of thrombi associated with pulmonary embolism, one that arises from a systemic vein and embolizes to the lung and a second that arises in the pulmonary artery distal to the embolus as a result of stagnant blood flow. As predisposing causes of venous thrombosis and pulmonary embolism, Virchow's triad consists of 1) stasis of blood, 2) venous injury, and 3) a state of hypercoagulability (9). This concept has proved valid in the development and direction of specific medical therapies to prevent or alter the course of venous thrombosis. The term "embolism" is credited to Virchow.

In 1872, Trendelenburg, a noted German surgeon and founder of the German Surgical Society, realized the sudden mortality associated with this condition while reviewing the deaths of 9 patients from pulmonary embolism at the hospital at Leipzig. He began experimental studies with pulmonary embolism in calves and perfected a surgical procedure using a left parasternal thoracotomy through which the pulmonary artery was opened and the embolus was removed. Trendelenburg treated two patients with this procedure but neither survived longer than 37 hours (10). Later Professor Martin Kirschner, a former pupil of Trendelenburg, performed the first successful pulmonary embolectomy in 1924 on a patient following a routine hernia operation. When Kirschner's case was reported at the German Surgical Conference in Berlin, Dr. Alton Ochsner, then a surgical resident, was in attendance and later noted that "the audience was electrified by the report." It became the custom in German clinics to have a surgical set in the rooms of patients in whom embolism was likely so that an emergency bedside Trendelenburg operation could be performed. Of course this constant bedside vigil was maintained by the young surgical registrars and residents in training (11). Because most of the patients did not die or require pulmonary embolectomy, this effort proved to be a tremendous waste of manpower and resources. Approximately 300 of these operations performed over the ensuing decade yielded less than 10 survivors (10). In his address to the American Surgical Association in 1944 Alton Ochsner stated, "I hope we will not have any more papers on the removal of pulmonary emboli before this organization, an operation which should be of historical interest only" (10). Dr. Ochsner later reflected "… how much better it would have been if they … prevented pulmonary embolism by ligating the vein on the cardiac side of the thrombus … to prevent detachment of the thrombus and its entrance into the heart and lungs" (11). Interestingly, while professors of surgery at Tulane, Alton Ochsner and Michael DeBakey advocated inferior vena caval ligation for prevention of pulmonary embolism as early as 1932 (12). It was Homans, however, who 2 years later performed proximal ligation of a femoral vein to prevent pulmonary embolism and is credited with the concept of prophylactic venous ligation (13).

Later Ochsner and DeBakey made the distinction between two types of venous thrombosis – thrombophlebitis and phlebothrombosis. They maintained that although thrombophlebitis is the more common form of venous thrombosis, pulmonary emboli rarely arise from this type due to inflammation and adherence of the clot to the venous endothelium. Phlebothrombosis, on the other hand, is frequently an extension of thrombophlebitis and has a high potential for embolization as it represents nonadherent red thrombus that propagates due to stasis and increased blood coagulability (14). To prevent pulmonary embolism, Ochsner emphasized prophylactic measures such as wrapping the lower extremities, early ambulation, electrical stimulation of calf muscles, head down position, and anticoagulation. Vena caval interruption by surgical ligation was stressed as a life-saving procedure in phlebothrombosis and also proved effective in preventing repeated episodes of pulmonary embolism (15,16). Sudden interruption of vena caval blood flow was sometimes accompanied by an immediate drop in cardiac output and troublesome later effects of chronic leg edema and post-phlebitic syndrome. To avoid these complications, partial plication of the vena cava by sutures or by specially designed clips was popularized in the 1960s by Adams, De Weese, and Miles (17-19).

Two surgical approaches evolved for the management of pulmonary embolism, operations that focused on removal of the embolus and operations designed to prevent embolization. In 1932, a young surgical resident and research fellow in Philadelphia, John Gibbon, Jr., observed a desperate but unsuccessful attempt at a pulmonary embolectomy by his mentor, Edward Churchill, to save the life of a young woman who had suffered a fatal pulmonary embolism. He surmised that the patient might have been saved if there had been a mechanism to take over her circulation and cardiorespiratory function. This event prompted Gibbon to work on the development of an extracorporeal circulation device while then a resident at Massachusetts General Hospital. Through his efforts a whole new era in cardiac surgery was born. On May 6, 1953, 21 years later, using the extracorporeal support machine which he had developed, he performed the first successful open heart operation, closure of an atrioseptal defect (20). It was not until April 18, 1961 that the first attempt at pulmonary embolectomy on extracorporeal circulation was carried out by Denton Cooley, then an associate professor of surgery at Baylor, on a woman recovering from an abdominal hysterectomy (21). The first successful pulmonary embolectomy on extracorporeal support was accomplished by Sharp 1 year later (22).

Paralleling the surgical advances in the management of pulmonary embolism were even more significant developments in the area of anticoagulation. As late as 1935, to prevent pulmonary embolism surgeons were using leeches that secrete a nontoxic substance, hirudin, which has anticoagulant properties. Needless to say, this treatment was unappealing and unacceptable to most patients. Citrate was used to anticoagulate blood as early as 1914 but only very small quantities could be tolerated in transfusion. In 1916, heparin was discovered by McLean, a medical student working on thromboplastins in the laboratory. Isolated from bovine lung and intestine, heparin required further refinement and purification, which was finally accomplished in 1932 (23). The utility of heparin in the management of thromboembolic disease was later confirmed clinically by Donald Murray, a surgeon and lecturer at the University of Toronto. His research on heparin was the subject of his Hunterian Lecture to the Royal College of Surgeons in 1939 (24). The discovery of heparin was pivotal in the management of thromboembolic disease and for the development of cardiovascular surgery and ultimately interventional cardiology.

Oral anticoagulants, such as dicumerol, did not appear until the 1940s. Today venous thrombosis and pulmonary embolism are primarily treated by systemic anticoagulation alone or in combination with thrombolytic agents such as urokinase, streptokinase, or tissue plasminogen activator. In the presence of recurrent pulmonary emboli in patients who have been adequately anticoagulated or when an embolus would most likely result in death, preventive surgical interventions are indicated. We owe a great deal of gratitude to David Sabiston, professor of surgery and chairman emeritus of the Department of Surgery at Duke, for his substantial contributions to our understanding of thromboembolism and its medical and surgical management. His numerous contributions have been cited in many of the references included in this article and in his monograph entitled "Pulmonary Embolism" (25).

Vena caval interruption by either surgical ligation or clip plication has yielded to less invasive intraluminal occlusive devices that are placed intravenously. The Mobin-Uddin umbrella device initially provided good results (26). Eventually, reports of complications surfaced, such as device migration, embolization, and perforation of the inferior vena caval wall. Over the last 30 years, a generation of new devices has developed rapidly. One of the most widely used is the Greenfield filter, which not only achieved a low recurrent pulmonary embolism rate of 3% but also has demonstrated a long-term patency of 98.5%, and the Gianturco-Roehm Birds' Nest (27,28). Although effective in preventing pulmonary emboli, these and other early venal cava filters were large, rather cumbersome, and often difficult to deploy. A "cut-down" on the femoral vein was required for insertion, and poor resolution, which existed in earlier radiographic imaging, made it difficult to properly deploy these devices. More recently, the availability of low profile, percutaneous filters such as the Simon-Nitinol filter and others has resulted in a shift from operative to nonoperative management of pulmonary embolism. Although not completely free from complications, interruption of the inferior vena cava with these highly effective, interluminal filters allows for excellent caval patency and protection from recurrent pulmonary embolism—and they do not usually require an open surgical incision for venous access (29).

The indication for open surgical embolectomy in massive pulmonary embolism has remained essentially unchanged through the years: persistent and refractory hypotension despite maximal pharmacological support in a patient with a clearly documented pulmonary embolus. Every effort to manage the patient by systemic heparinization, ionotropic agents, vasopressors, ventilatory support, and oxygen supplementation should be undertaken. The use of thrombolytic therapy must also be considered. Percutaneous mechanical thrombectomy, utilizing a rheolytic venous thrombectomy device (Angiojet®, Possis Medical, Inc., Minneapolis, MN) driven by a high-velocity saline jet and Venturi effect evacuation system, may also be considered as it has demonstrated some success in the treatment of massive pulmonary embolism (30).

Once the surgical approach is elected, the pulmonary embolectomy is performed with the patient on full cardiopulmonary bypass support through a sternotomy incision. Postoperative complications that may be associated with this approach (essentially a modified Trendelenburg procedure) include endobronchial hemorrhage, reperfusion pulmonary edema, acute right ventricular failure, and recurrent pulmonary embolism (31). Mortality following this procedure has been reported to be 37.5% (32).

Venous thrombosis and resulting pulmonary embolism usually present as an acute disorder. However, chronic recurrent or subacute pulmonary emboli may occur and cause obliteration of the pulmonary arteries resulting in pulmonary hypertension and right-sided heart failure. Patients with this problem who have significantly elevated mean pulmonary artery pressures have a poor survival. The 5-year survival in patients with a mean pulmonary artery pressure greater than 30 mmHg and 50 mmHg is 30% and 10%, respectively. Some of these patients who have proximal pulmonary arterial obstruction and patent distal arteries may be candidates for pulmonary endarterectomy (33). Pat Daily of San Diego first reported successful bilateral pulmonary thromboendarterectomy in 1987. In 1989, he and his colleagues

outlined the technique of thromboendarterectomy in 100 consecutive patients in whom he employed cardiopulmonary bypass, deep hypothermia, and circulatory arrest (34,35). The mortality associated with this procedure is reported to be 8.7% even in the most experienced centers (36). Those who respond to therapy can expect a significant improvement in functional capacity and oxygen saturations and a decrease in pulmonary arterial pressure. Adequate systemic anticoagulation postoperatively is imperative in preventing recurrent emboli and post-thromboendarterectomy pulmonary arterial thromboses (37).

Venous thrombosis and pulmonary embolism remain a major cause of morbidity and mortality today. A high index of clinical suspicion of the presence of thromboembolic disease serves to initiate prompt evaluation and early treatment, which often proves to be life-saving for the patient. The classical physical signs and clinical symptoms in a patient in whom Virchow's triad likely exists remain reliable indicators of the possibility of thromboembolic disease. Fortunately, we now have many more diagnostic and therapeutic options that were simply not available 2 decades ago. Treatment of pulmonary embolism and venous thrombosis has changed from therapeutic surgical management to primarily preventative medical management. A great deal of gratitude is owed to the many historical figures and pioneers who have contributed to our knowledge, understanding, and treatment of the common and often lethal condition of pulmonary thromboembolism.

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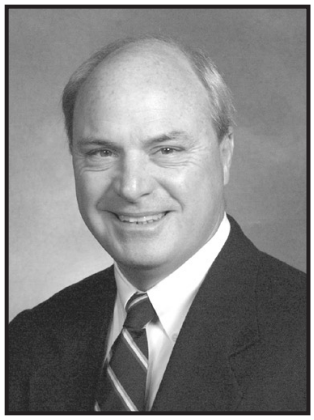

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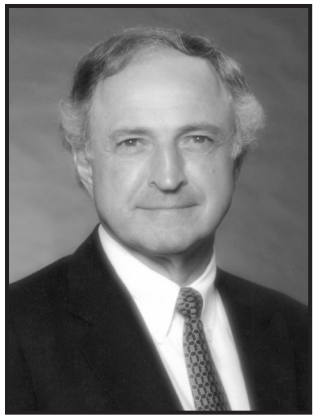

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