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Fatal post-operative pulmonary embolism

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FATAL POST-OPERATIVE PULMONARY EMBOLISM

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by

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INTRODUCTION

Over every surgical patient, even after apparently
very minor procedures, there hangs the Damoclean sword of fatal
pulmonary embolism. No complication of surgery is more tragic
since it is so sudden and unpredictable, striking down the strong
as well as the weak. Although the medical profession in the past
has seemed to adopt a somewhat fatalistic attitude toward this
problem, it seems justifiable in the light of recent promising
developments to review the subject and to point out the progress
that is being made.

Statistics regarding the frequency of pulmonary
embolism are notable chiefly for their great variation. Accord-
ing to Belt (1) statistical studies of the incidence of pulmonary
embolism are open to criticism on grounds that figures from some
clinics are more carefully compiled than others. In this author's
series of 567 posts, 11 deaths (1.9%) were due to postoperative
pulmonary embolism and he states that pulmonary emboli are found
in 10% of autopsies in adults. An extremely large series of
cases, 316,060, collected by Collins (2) from the literature
showed the incidence of postoperative pulmonary embolism to be
.53%. Barnes (3) cites his statistics more dramatically. He
estimates that 33,748 people die from pulmonary embolism yearly
in the United States and it may be assumed that 3,060,000 people
now living in this country will die eventually of pulmonary

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embolism. According to this author, pulmonary embolism accounted for 6% of all surgical deaths at the Mayo Clinic from 1917 to 1927 and for 5.8% of all surgical deaths from 1931 to 1937 despite all efforts at prevention.

Snell (4) found that pulmonary embolism ranked third among causes of postoperative death at the Mayo Clinic from 1920 to 1925. His figures show that peritonitis accounted for 18.3%, pneumonia 13.8%, and pulmonary embolism 7.9% of postoperative deaths.

According to Gibbons (5), approximately 1 out of every 500 patients operated on dies of pulmonary embolism, and 8 out of every 100 postoperative deaths are caused by pulmonary embolism.

From the figures cited above it can readily be seen that pulmonary embolism as a cause of death following operation is by no means as rare as is commonly believed, since it accounts for from 6 - 8% of all postoperative deaths.

PATHOLOGY

Virchow (6) in 1846 was the first clearly to describe pulmonary embolism and to correlate the relationship between thrombosis and pulmonary embolism. This great work was completed before "the father of modern pathology" was twenty-six years of age. The views held at that time in regard to the occlusion of the pulmonary arteries by clotted blood were summarized by Virchow as follows:

"1. Blood clotting occurs as a result of compression of a branch of the pulmonary artery at some point as when an artery is ligated.

2. A harmful substance or an irritation transmitted from adjoining structures by continuity of parts, sets up an inflammation in such a vessel, and this brings about clotting of a column of blood.

3. The blood clots spontaneously without a mechanical obstacle and without the agency of the vessel walls; the agency for clotting lies in the blood itself or in some elements mixed with it.

4. The occlusion results from a more or less compact mass which is brought by the circulation to the pulmonary arteries and there impacted."

Virchow refers to the first three theories as "quite hypothetical assumptions" and proceeds to prove the embolic

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theory by the following facts.

"1. As often as I have found plugs on the pulmonary artery I have always been able to demonstrate plugs also in the venous system leading thereto (including the right heart).

2. The plugs in the pulmonary artery when young fill the entire diameter of the branch involved without adhering to the walls and without alteration of the texture of the latter.

3. In the majority of cases the plugs do not originate in the capillaries, but extend a certain distance into the pulmonary artery usually being seated at the dividing point of a large vessel or riding the bifurcation.

4. The age and degree of metamorphosis of these plugs corresponds in general with the condition of the venous plugs.

5. When the blood within a vein clots, the coagulation extends as a rule not simply to the next vessel maintaining circulation but across its mouth and a greater or less distance into its lumen. On account of its great wetness this part has always a marked tendency to softening; after a certain time, accordingly, the blood streaming against it will be able to loosen it and free portions from it.---However, I have had the good fortune to observe cases where the capping pieces torn from the end of clots, although removed to a greater or less distance were still to be found and it was easy to prove from their upper concave, lower convex and reverse stair like surface that they had been separated from a particular place."

Since Virchow's work there has been little of fundamental importance added to his excellent description of pulmonary embolism. Virchow thought that retardation or standstill of the blood-stream was the important factor in causing intra-vascular clotting. However, Cohnheim (7) pointed out the importance of abnormalities and injuries to the endothelial of the vessel wall as an intrinsic cause of the coagulation. He states, "That retardation of the blood stream and still more standstill of the circulation at the same time favours the occurrence of coagulation cannot of course be denied; yet this goes for nothing in the absence of such conditions as are actually in a position to produce coagulation; where no such are present a thrombosis of stagnation cannot occur."

Welch (8) in 1909 published an extensive review on the subjects of thrombosis and embolism. He recognizes three classes of causes assigned for thrombosis, namely, alterations in the blood, mechanical disturbances of the circulation and lesions of the cardiac or vascular wall. He emphasizes the importance of phlebitis in causing thrombosis, a factor which had been neglected because of Virchow's opinion that the changes in the vein walls were always secondary. Welch also discusses the role of increased fibrinogen and blood platelets in causing coagulation but draws no definite conclusions as to their relative importance. In his opinion disturbance of the circulation and changes in the vascular walls are the determinants of the localization of thrombi; while

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changes in the chemistry and morphology of the blood are important predisposing causes. Welch states that the effects of pulmonary embolism vary with the size of the plugged vessel, the rapidity and completeness of its closure, the nature of the embolus, and associated conditions. He distinguishes embolism of large, of medium-sized and small arteries, and of capillaries. Sudden or rapid death follows embolism of the trunk or of both main divisions of the pulmonary artery. It may occur also from embolism of only one of the main divisions or from plugging a large number of branches at the hilum of the lung. After an excellent description of the symptoms Welch states, "There has been much and rather profitless discussion as to the degrees on which the symptoms are referable to asphyxia, to cerebral anemia or to interference with coronary circulation. Doubtless all three factors are concerned, but the exact apportionment to each of its due share in the result is not easy, nor very important." He emphasized the importance of careful dissection of the peripheral veins in order to find the site of origin of the embolus.

Aschoff (9) described in detail the morphological structure of thrombi and the mechanics of thrombus formation. He pictures the thrombus as beginning with the deposition of blood platelets on the intima of a vein. The blood stream is, therefore, slowed and leukocytes are deposited around the platelets, thus forming a white thrombus. The thrombus grows into the venous stream as a sponge-like mass of dead platelets which

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excites coagulation, so that leukocytes, red cells and fibrin are soon entangled in its tough meshes. At first the process does not close the vein, but when the body of the thrombus has been built out from the adherent head, the vessel is soon filled with a mixed, dark-red solid mass. As the thrombus extends up and down the vein, its youngest portion, or tail, is seen to be soft and clot like having no longer a supporting frame of plate-lets and is easily broken up and carried away. A thrombus tends to grow until it meets a vigorous stream and thus its proximal end is likely to heal at the point where a branch carrying a strong current enters the thrombosed vessel. According to Aschoff two conditions are necessary for the deposition of blood platelets which initiates thrombosis. One is retardation of the blood stream, the second being increased agglutinability of the blood platelets. He says, that unfortunately we have no knowledge of the sponta-neous changes occurring in this property of agglutinability.

Aschoff considers changes in the vessel wall, altera-tions in cardiac action and loss of blood during operations as indirect factors in thrombosis. He agrees with Virchow in minimizing the importance of infection and emphasizing the im-portance of blood stasis in the causation of thrombi. Most pulmonary emboli are considered by Aschoff to arise from the femoral vein. He mentions certain anatomical peculiarities favor-ing this when the body is lying prone. For example, the femoral vein just where the large valves are present lies close under

Pouparts' ligament resulting in a bend in the path in which the blood flows. Also when lying on the back the increased compression of the left iliac rein by the arterial trunks (right iliac, middle sacral and left hypogastric arteries) has a direct influence in slowing the stream and explains the frequency of thrombosis in the left lower limb.

Homans (10) says there is good reason to believe that outspoken processes such as phlegmasia alba dolens or thrombosis in varicose veins are less apt to cause embolism than the quieter ones. In the case of phlegmasia alba dolens, inflammatory changes tend to fix the thrombus and the collateral current called forth by obstruction of a considerable length of the main venous trunk would seem to offer little opportunity for the formation of the long, fragile, clot-like detachable tail. Again in the case of varicose veins the sclerosed state of the vein, overstretching of its coats by rapid dilatation, perhaps the presence of bacteria in its wall combine to make a thrombus adhere solidly. The explanation is offered that the less the vein's wall is inflamed or injured previous to the onset of and during the course of thrombosis the greater is the probability that an insecure propagating thrombus will be established and that a fatal pulmonary embolus will occur. According to Homans, the most available sources of pulmonary embolism are in the femoral system and the deep veins of the pelvis. A propagating clot may project from a vein of the deep calf or popliteal space into the femoral, from

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the femoral into the external and common iliac, from pelvic veins
through the hypogastric into the common iliac and vena cava and
from the common iliac into the vena cava. Homans especially
emphasizes the importance of thrombosis of the deep veins of the
lower leg which he believes carries a high incidence of pulmonary
embolism.

EXPERIMENTAL WORK

Virchow in establishing the doctrine of embolism showed in a celebrated series of experiments (7) that the blood stream can actually carry off with it solid bodies even when these are large and comparatively heavy such as bits of muscle, fibrinous coagula, india-rubber and even quicksilver, and thus put beyond doubt that thrombi, to say nothing of substances specifically lighter such as fat drops, colonies of bacteria, etc., are tranportable.

Church (11) in 1892 wrote concerning Von Swieten who "140 years ago did animal experiments producing pulmonary thrombosis and embolism."

The more recent experiments have been concerned chiefly with the study of the mechanism of death in pulmonary embolism and the amount of occlusion of the pulmonary artery necessary to produce death. In general these experiments have been of two main types, (1) occluding the main pulmonary artery and branches by ligation or compression and (2) injecting particulate objects intra-venously.

Mann (12) injected emboli made of paraffin and the animals own blood into the venous circulation of dogs. Death did not occur until the pulmonary circulation was practically occluded. Results were the same whether the blood pressure of the animal was normal or depressed by ether or disease and

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whether the procedure was carried out under ether or local.

Haggart and Walker (13) produced partial or complete block of the pulmonary artery in the normally breathing animal by using clamps. Clamping the left branch of the pulmonary artery caused an immediate rise in pulmonary pressure averaging about 29% and an increase in pulmonary ventilation of about 25% but no significant effects on general systemic pressure, size of the heart, heart rate or heart output. Following total pulmonary occlusion a severe and immediate reaction sets in. The heart dilates quickly, the pulmonary pressure rises sharply and then gradually falls, systemic pressure falls while the respirations become irregular and finally cease altogether. The point at which failure occurred is sharply defined since beyond this end-point a circulatory collapse is precipitated by a minute increase in the arterial obstruction but if this is not applied no untoward change results.

Moore and Binger (14) produced embolism of pulmonary arterioles and capillaries by injecting starch grains intra-venously. This was associated with respiratory and circulatory changes other than those occurring with occlusion of the main pulmonary artery. The main difference was the occurrence of rapid shallow breathing in starch embolism which the authors considered was caused by the secondary pathological changes, congestion and edema in the lung parenchyma in this form of embolism. These results suggest that some caution should be

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used in comparing the results of experiments producing pulmonary occlusion by compression or ligation with those producing occlusion by injecting particulate objects intravenously.

The generally accepted theory that pulmonary embolism produces death by acting as a mechanical plug is pointed out by Barnes (3) as being not entirely satisfactory. Correlation between size of the embolus and the fatal issue is lacking since at times a relatively small embolus is sufficient to cause death.

Barnes (3) cites the work of Villaret and his co-workers who produced emboli experimentally. They found that (1) section of the vagus nerve of rabbits increased seven times the quantity of embolic particles necessary to produce death; (2) section of the cervical sympathetics dimished four times the quantity of embolic particles to produce sudden death; (3) atropine and ephedrine delayed death perceptibly and atropine plus $NaHCO_3$ delayed death still more; (4) HCl rendered the animal more susceptible. The conclusions reached were that sudden death resulted from reflex sympathetic inhibition, and that alkali and acid may be important.

Gosset, Bertrand and Patel (3a) also showed by experiments that the embolus was lodged in the pulmonary artery by spasm. They believed death was due to reflex spasm of all arteries at the hilus of the lungs. The reflex spasm theory is the basis for the use of papaverine in the treatment of pulmonary embolism which will be referred to later in this thesis.

However, this theory is contradicted by the results obtained by Hall and Ettinger (15) in their experimental study of pulmonary embolism. These observers found that (1) clamping a main branch of the pulmonary artery raises the pulmonary arterial pressure without any reflex inhibition to the heart. The aortic pressure falls for a brief time but is quickly restored to normal while the pulmonary rise lasts as long as the obstruction. (2) The main pulmonary artery may be compressed to 75% occlusion without causing death. (3) Total occlusion of the main pulmonary artery causes death. Release of the ligature within 93 seconds is followed by recovery. (4) Distention of a main branch with total occlusion does not produce death or any reflex referable to the heart. (5) Distention of a main branch or of the main artery without occlusion does not cause death or any cardiac reflex. (6) Plugging of a main branch with embolus does not cause death. (7) Plugging of most of the peripheral branches does not cause death. (8) Plugging of main pulmonary artery or of valve orifice causes sudden death due to purely mechanical effects. These results do not support the theory that death from pulmonary embolism is due to reflex effects. To quote the authors, "Death in man is said to follow plugging of a main branch without sufficient obstruction to suspend circulation through the other lung. It may be inferred that either (a) death in man is accomplished by some nervous or other mechanism not found in the dog, or (b) autopsy examinations in man have not included a careful inspection

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of the cavity of the right ventricle for clots which may have plugged the pulmonary orifice." On the basis of post mortem observations in dogs the authors suggest that many emboli in man may plug the pulmonary orifice without leaving the right ventricle, cause death by obstruction and be incorporated in what may be regarded as post mortem clot while death may be attributed to smaller emboli lodged further along in a branch of the artery. The emboli in these experiments were produced by fixing blood clots in 10% formalin.

Gibbon et al (16) studied the changes in circulation produced by gradual occlusion of the pulmonary artery. Their results differed from those of previous investigators who had found that the circulation is normal to a critical point and then death occurs suddenly due to circulatory failure. Gibbon found that, (1) Obstruction of the pulmonary artery up to 60% of its cross-sectional area is without significant effect upon the arterial or venous pressures. (2) Reduction in cardiac output attended by a fall in blood pressure and rise in venous pressure occurs when occlusion lies between 60% and 85%. (3) Circulation fails not primarily from cardiac insufficiency but due to the fact that blood collects on the venous side of the system by reason of obstruction to outflow from the right heart. (4) Obstruction is fatal when 85 - 100% of the pulmonary artery is occluded. Gibbon attributes the difference in his results to the use of a clamp on the pulmonary artery which was capable of

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much finer adjustments than the clamps used by previous investigators.

Gibbon (17) has also done some very ingenious experiments in which the circulation of dogs was artificially maintained during partial or complete occlusion of the pulmonary artery. The means employed were the withdrawal of blood from a peripheral vein, introduction of O_2 into that blood and reinjection of the blood into a peripheral artery in a central direction. Blood was thus short circuited around the obstruction in the pulmonary artery and part or all of the work of the heart and lungs was temporarily taken over by artificial means. Life was maintained in these animals for short periods of time (up to $2\frac{1}{2}$ hours) during complete obstruction. These animals have recovered and are alive and normal months later.

Mendelowitz (18) in some recent experiments has carefully studied the course of changes in the circulation accompanying pulmonary embolism. He objects to methods previously employed to produce pulmonary obstruction experimentally since (1) external compression or ligation requires an extensive surgical approach while (2) injecting particulate matter intravenously entails the obstruction of many smaller branches. Mendelowitz devised a method in which endovascular obstruction of the main pulmonary artery could be produced in 92% of trials. This consisted of introducing into the internal jugular vein an embolus formed by filling Penrose tubing with fluid barium sulfate. The course of the embolus

could then be followed by x-ray to the pulmonary artery. He concluded that death was probably caused by anoxia of the brain or of the heart with secondary acute heart failure or both. Anoxia was attributable primarily to a decrease in cardiac output and secondarily in some to arterial anoxemia. The decrease in cardiac output in pulmonary embolism is caused by major obstruction in one portion of the double circuit which constitutes the mammalian blood vascular system and therefore represents a hitherto unemphasized distinct form of shock. This author also noticed characteristic changes in the ST segment or T waves of the EKG during pulmonary embolism.

The results obtained by Hall and Ettinger, Gibbons, and Mendelowitz seem to prove quite conclusively that death from pulmonary embolus is due primarily to its acting as a mechanical block and not from any reflex effects.

Before leaving the subject of experimental pulmonary embolism the bacteriological studies of Rosenow (19) should be mentioned. Rosenow isolated a diplostreptococcus from five fatal cases of pulmonary embolism and demonstrated the organism microscopically in twenty-five cases. This organism is of low virulence and with pure culture, thrombosis sometimes associated with pulmonary embolism, has been produced experimentally in three species of animals. Rosenow concluded that this diplostreptococcus is the common cause of postoperative and non operative thrombi leading to fatal pulmonary embolism. In the light of these experiments

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he believes that stasis and other factors generally considered
as causes of this condition appears to be merely contributory.
The immunity found to exist in animals 10 to 14 days after a
series of injections suggests the possibility of a means of pre-
vention through specific inoculation with a vaccine prepared
from this organism. Unfortunately, these rather startling
results have not been confirmed by other observers.

CLINICAL SYMPTOMS

The symptoms of pulmonary embolism are very typical so that little time needs to be spent in describing them. The clinical picture is well described by Welch (8) as follows: "Death may be instantaneous from syncope. More frequently, the patient cries out, is seized with extreme precordial distress and violent suffocation and dies in a few seconds or minutes. Or when there is still some passage for the blood, the symptoms may be prolonged for hours or even days before the fatal termination. The symptoms of large pulmonary embolism are the sudden appearance of a painful sense of oppression in the chest, rapid respiration, intense dyspnea, pallor followed by cyanosis, turgidity of the cervical veins, exopthalmos, dilation of the pupils, tumultous or weak and irregular heart action, small empty radial pulse, great restlessness, cold sweat, chills, syncope, opisthotonos and convulsions. The intelligence may be preserved or there may be delerium, coma, and other cerebral symptoms. Particularly striking is the contrast between the violence of the dyspnoea and the freedom with which the air enters the lungs and the absence of pulmonary physical signs; unless in the more prolonged cases it be the signs of oedema of the lungs. Recovery may follow after the appearance of grave symptoms."

Churchill (20) describes a typical venous pulsation above the clavicles which can be seen in many cases of pulmonary

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embolism.

According to White (21) sudden great obstruction to
the pulmonary circulation results in the acute Cor Pulmone, i. e.
dilatation of the pulmonary artery and right heart chambers.
This results in characteristic early signs of embolism. Increased
prominence and pulsation is noted by inspection and palpation in
the second and third intercostal spaces just to the left of the
sternum. There may be a loud systolic murmur and an increased
pulmonic second sound. Later, there may be a friction rub in the
same region and gallop rhythm heard along the left sternal border
due to dilatation of the right ventricle.

X-rays were not obtained at the height of the trouble
but in those surviving they usually showed pulmonary infarction
later. White believes the EKG records are typical and can be
used to differentiate pulmonary embolism from coronary thrombosis.
He discusses the differential diagnosis of pulmonary embolism
from coronary thrombosis, dissecting aneurysm, pulmonary collapse,
spontaneous pneumothorax and pulmonary edema.

Averbuck (22) discusses the differentiation of acute
coronary thrombosis from pulmonary embolism. He says that pul-
monary embolus may cause a clinical picture indistinguishable
from acute coronary thrombosis and names the following points
which may help in difficult cases.

1. Females without hypertension or diabetes
   are likely to have embolus.

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2. Post-operative cases are likely to be
   embolus.

3. A previous history of coronary disease.
   would suggest coronary thrombosis.

4. Marked cyanosis and dyspnea suggest embolus.

5. In some cases of pulmonary embolus there
   may be typical right chest pain, pleural
   rubs and later hemoptysis.

Averbuck says x-rays are usually not possible to get
due to the grave condition of the patient ahd the EKG findings
are not definite.

According to Barnes (23) cyanosis and dyspnea are not
always present in pulmonary embolism. The pain of pulmonary
embolism is usually referred to the lateral regions of the
thorax and made worse by inspiration. He observed a number of
patients and obtained characteristic EKG changes.

PREDISPOSING FACTORS

Barnes (3) states that the multiplicity of hypotheses
to explain the occurrence of pulmonary embolism is an indication
on the one hand that the cause is not known, and on the other
that several causes acting in combination are a more likely ex-
planation. In spite of the ignorance of a definite cause for
pulmonary embolism, many so-called predisposing factors have been
advanced on the basis of clinical study. Although some of these
factors seem to definitely predispose to the formation of thrombi
and emboli, it is probable that most of them have little if any-
thing to do with their formation. The necessarily small number
of cases presented by most authors on the subject makes it dif-
ficult to draw any definite conclusions.

Many writers state that patients who die from pulmonary
embolism after surgery are older than the average surgical
patient. Vance (24), in a series of 90 cases, found that 50% of
the patients were from 40 to 60 years old. A similar age incidence
was found in Russum and Kemp's cases (25). However, in McCartney's
(26) series of 73 cases the age varied from 19 to 83 years. When
considered in relation to the number of necropsies in each decade,
this series shows practically the same incidence of embolism in
all decades after the first. McCartney believes age is not so im-
portant a factor as it is usually thought to be.

Pulmonary embolism seems to be almost equally divided

among males and females. McCartney's series included 40 males and 33 females while Vance's series included 37 females and 23 males.

Snell (4) found a high incidence of pulmonary embolism as a cause of postoperative death in obese patients. This suggests but does not prove that obesity increases the liability to pulmonary embolism. The difficulty of operation with unusual trauma may be a factor and mild circulatory failure with resulting venous stasis might be more common in obese persons. Snell also advances the possibility that after operation on obese patients, there may be an increased liberation of thromboplastic lipoid substances such as kephalin due to the extensive areas of fat invaded.

Kuhn (27) of the Institute of Pathology at Freiberg reported that the incidence of fatal embolism in Germany from 1924 to 1927 increased from 1.3% to 4.9%. He stated his belief that this increase in the incidence of thrombosis and embolism is the result of prolonging life by the treatment of patients with diseases of the heart. However, Rosenthal (28) failed to find a parallel increase in the incidence of thrombosis and embolism on the basis of reports from the United States and Canada. Belt (1) regards circulatory embarrassment as of prime importance in the etiology of venous thrombosis and pulmonary embolism. He found that a high per cent of postoperative fatalities showed evidence of minor degrees of cardiac incompetence and attributes

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this to the slowing of blood in the veins when the heart action is impaired. Henderson (29) found in his series of cases of postoperative pulmonary embolism that as a group they had normal or somewhat subnormal blood pressure.

Homans (10) believes that the retardation of blood flow following operation is usually due to mechanical causes rather than debilitating disease or enfeeblement of the heart. He sums up the disorders of venous return as follows: the difficulty of forwarding blood from the legs is increased by a reclining position in bed, especially if the legs are flaccid; it is aggravated by increased abdominal tension and pelvic congestion; and because of confused currents in the upper calf and at the groin, a slow stream is especially likely to lead to thrombosis at these points; finally a slow current once thrombosis has taken place favors the formation of a dangerous propagating clot, just as a brisk current discourages such a process.

The drop in pulse rate and blood pressure and splinting of the body and abdomen by the painful incision are emphasized by Robertson (30) as factors causing stasis. Walters (31) mentions the interference with circulation by intra-abdominal manipulation and the 48 hours of intestinal quiet after intra-abdominal operations, while Bancroft (32) maintains that tight abdominal bandages are an important factor in causing slow venous flow.

Dehydration is considered by Bancroft (32) and Homans (10) to be an important factor leading to thrombosis. Individuals

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who have become anemic because of bleeding uterine fibroids, those who have become depleted by vomiting, by sweating and failure of fluid intake in connection with an abdominal operation, perhaps those also who have suffered serious malnutrition from any cause are more liable than others to thrombophlebitis.

Studies on changes in the blood itself, which are probably the fundamental cause of thrombosis and embolism formation, have been rather disappointing. Allen (33) studied the post-operative changes in the blood of 12 patients. He found that the number of platelets, cholesterol, bleeding time, coagulation time and blood calcium did not show significant variations. The number of erythrocytes and leukocytes, prothrombin time, fibrinogen and lipoids showed definite and constant changes. The sharp constant increase in fibrinogen postoperatively may cause an increased size and strength of the clot. The increase in leukocytes may be of importance because leukocytes furnish thromboplastic substances important in coagulation of the blood. Allen found the prothrombin time to be prolonged and a decrease in lipoids postoperatively but states that the significance of these findings is not clear. He summarizes these findings by stating that, with the possible exception of the lipoids, there is a non-specific physiological response to operation which occurs independent of the clinical or surgical status of the patient. This non-specific physiological change produces changes in the blood which may partially explain the high incidence of pulmonary embolism in surgical as compared

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with non-surgical patients. There is probably in every surgical patient a definite increased potentiality for intra-venous coagulation by virtue of these changes, but this in all probability plays a minor part in comparison with other factors in actual deposition of the clot and subsequent pulmonary embolism.

Pickering and Mather (34) offer the theory that the ingress of broken tissue juices into the circulation may induce hypercoagulability and an increase of the platelets in the blood which in turn are important participants in the inception of thrombosis. However, they admit that this only holds true when the condition of the blood plasma favours the deposition and clumping of platelets.

Although Allen (33) did not note any change in the number of blood platelets after operation, Galloway (35) noted a definite increase in the number of platelets four to fifteen days after fracture in ten cases. Brock (36) reported a case in which thrombosis occurred coincident with the maximum postoperative rise in platelet count. He believes that this increased platelet count is the precipitating factor in thrombosis formation and is also important in accelerating the rate of formation of the clot.

Infection has been mentioned as a factor predisposing to thrombosis and embolism by Rosenthal (28), Bancroft (32) and Henderson (29). McCartney (26) noted wound infection in 17 of 31 cases of postoperative pulmonary embolism. Vance (24) in studying the microscopic sections of thrombosed veins in cases who had died

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of pulmonary embolism noted phlebosclerosis, subacute phlebitis or periphlebitis in all sections. Barnes (3), however, claims that there is little evidence that pulmonary embolism arises from the thrombus of thrombophlebitis. Ochsner and Debakey (37) believe it is necessary to differentiate between thrombophlebitis and phlebothrombosis. In the former intravascular clotting is associated with and dependent on inflammation of the wall of the vein but in the latter there is no associated inflammatory process and because of the absence of fixation of the thrombus to the vessel wall there is great danger of embolism.

The type of operation seems to definitely play a role in the formation of postoperative pulmonary emboli. Aschoff (9) mentions the frequency of such emboli as a result of gynecological or obstetrical operations. Belt (1) found that of 11 cases, 6 had laparotomies, 3 fractured femurs, 1 an injection of varicose veins and 1 a transurethral prostatectomy. McCartney (26) found that postoperative pulmonary embolism usually follows operations below the level of the diaphragm and only rarely above the diaphragm. It is most common after operation on the prostate, the intestine and the biliary tracts. David (38) quotes interesting statistics which show that 1 pulmonary embolism occurs in every 100 cases after resection for carcinoma of the stomach, 5 out of every 100 resections for carcinoma of the rectum and 2 of every 1000 cases of appendectomy. He also points out the fact that 50% of pulmonary emboli have their source in the femoral or iliac

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veins usually not in the immediate operative field.

Vance (24) pointed out the occurrence of pulmonary embolism after various forms of trauma to the lower limbs. The degree of trauma varied from mere contusions or abrasions to severe fractures, and in the large majority of instances, the causal thrombosis was found on the side of the injury. Vance believes the basic cause of thrombosis in these cases is a vein of the lower extremity either diseased or a locus resistentis minorae and so prone to develop thrombophlebitis readily under slight provocation. McCartney (39) found embolism after trauma occurred more often in females than males and suggested this was due to the higher incidence of varicose veins in females. Homans (40) calls attention to the thrombosis of the deep veins of the lower leg after minor injuries below the knee. He claims that the incidence of fatal pulmonary emboli is high in this condition.

REVIEW OF HOSPITAL CASES

A series of 21 cases of pulmonary embolism from this
hospital were reviewed briefly in an attempt to find some common
predisposing factors. Of these 11 patients had undergone operation
(including delivery), 9 were medical patients, and 1 was post-
traumatic after a fractured ilium. Thirteen males and 8 females
were represented, their ages varying from 14 to 78. In the medical
cases the average age was 50 years and in the surgical group 52
years. Four of the patients had evidence of organic heart disease
and 4 had malignancies.

In the surgical patients the importance of trauma in
the pelvic region is well brought out by the fact that 7 of the
11 patients had operations, including delivery involving trauma
around the pelvis. The types of operation included normal de-
livery 3, bilateral herniorraphy 1, partial resection of stomach
1, choleycystectomy and appendectomy 2, perineal resection of
rectum 1, radical mastectomy 1, repair of anal sphincter 1,
colporraphy 1. This series also exemplifies the fact that opera-
tions causing comparatively little trauma such as normal delivery,
herniorraphy, etc., are just as potent in causing pulmonary em-
bolism as more major procedures. Apparently it is the fact of
trauma and not the degree of trauma which is the determining factor.

The general condition and constitution of these patients
was noted as good in 4 of these 11 surgical cases, while in only

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2 cases was the general condition especially poor. Obesity
was present in only 4 of these patients.

The postoperative temperature in these patients seemed
higher than one would normally expect. However, the significance
of this cannot be evaluated unless control determinations are
studied on other postoperative patients. It is interesting to
note that in 3 of these patients postoperative exercises and deep
breathing was carried out but in spite of this pulmonary embolism
developed. The average postoperative day of death varied from 2
to 79 days with an average of 15 days. The post traumatic death
occurred 6 days after the fracture of the ilium.

The origin of the embolus was found in only 8 of the
21 cases. Of these 8, 2 originated in the right femoral veins,
3 in the iliacs, 2 in the pelvic veins, and 1 in the inferior
vena cava. In only 3 of the total of 21 cases was there clinical
evidence of thrombophlebitis before death.

It is obviously impossible to draw any conclusions from
such a small series of cases, but certain interesting facts were
brought out. About the only factor common to all patients was the
fact that they were bedfast since they represented almost every
conceivable variety of age, sex, general condition, weight and
disease. There is a strong indication that trauma to the pelvis
even of a slight degree is a potent factor in setting off the
thrombosis and embolism, and there may have been some significance
to the postoperative rise in temperature.

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TREATMENT

Prophylaxis

The discussion of treatment for pulmonary embolism
will be divided into prophylactic, surgical and medical. Pro-
phylaxis is by far the most important treatment and quite properly
the one most often mentioned by authors on the subject. Unfor-
tunately, as Gibbon (5) points out, there is as yet no specific
measure for the prevention of postoperative thrombosis. Barnes
has stated (3) that from 1917 to 1927 pulmonary embolism accounted
for 6% of all surgical deaths at the Mayo Clinic. From 1931 to
1937, 5.8% of all surgical deaths were due to pulmonary embolism
despite all efforts at prevention. Measures directed to the
prevention of pulmonary embolism are aimed first toward the pre-
vention of thrombosis and next toward the prevention of embolism
if thrombosis occurs. The prevention of thrombosis is mainly an
attempt to eliminate those predisposing factors toward thrombosis
already described. Since venous stasis is the most generally
accepted predisposing factor, it is the factor which is most
vigorously attacked. Robertson (30) uses massage, motion and heat
to the lower limbs as well as encouraging an increased respiratory
rate. Barnes (3) suggests the use of CO_2 postoperatively to en-
courage deep breathing and favor venous return. Bancroft (32)
stresses the prevention of increased intra-abdominal tension.
He insists that abdominal wounds be so carefully closed that

tight strapping and binders are not necessary and he regards the prompt restoration of intestinal tone by the early use of semi-solid or solid food as essential.

G. Walters (31) recommends the use of thyroid extract to increase metabolism, the rate of blood flow and blood pressure after operations. He reported the results of using thyroid in 4500 surgical patients and reported no fatal emboli in patients in good general condition with this regime. Kvale, Smith and Allen (41) recently studied the speed of blood flow in the lower extremities in various conditions. They found that hyperthyroidism, elevation of the extremities and exercise increased the speed of blood flow. These results confirm the rationale of using thyroid, elevation and exercise postoperatively to prevent venous stasis. However, the effectiveness of these measures in preventing thrombosis can only be judged after a long period of time.

Mills (42) presented evidence of the relation of food intake to blood coagulability, pointing out the increased coagulability following protein intake and the lack of such effects with carbohydrate and fat. He, therefore, suggests that all patients should be kept on a very low protein diet for the first two weeks following operation, trauma or other conditions likely to result in thrombosis and embolism.

Bancroft, Brown and Quick (32) have devised a clotting index as a measure of the threat of thrombosis. The formula used is given below.

$$\frac{(Prothrombin)\ (Fibrinogen)}{Antithrombin} = .6$$

An index over 1 points to a tendency to thrombosis and the need
of preparing the patient by the use of a high carbohydrate, low
fat and protein diet. Sodium thiosulphate in 10% solution is
given intravenously in these cases in the belief that it will
decrease the blood coagulability. Bancroft also emphasizes the
importance of combatting dehydration.

Bankhoff (43) injected patients with 1 cc. of thyroxin
two days before operation. In sensitive patients, after three
hours there was an increase in temperature, pulse and respiration,
and increase in erythrocyte count and a decrease in platelet
count in sensitive patients. In non-sensitive patients there was
no change and these patients were thought especially liable to
thrombosis formation. In these patients Bankhoff used atropine
and "ephetonin" for five days postoperatively and reported no cases
of thrombosis or embolism in these patients. In attempting to con-
firm these results, Pilcher (44) used this regime prophylactically
against thrombosis and pulmonary embolism. He treated patients
following trauma and operation for periods of five to nine days
with atropine and ephedrine, but noted no change in the incidence
of thrombosis and embolism.

The treatment of an established venous thrombosis of a
lower extremity customarily consists mainly of absolute immobility
in order to prevent the detachment of emboli. All unnecessary

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movements and manipulations are avoided since a large number of deaths from pulmonary embolism have occurred when the patient first walks or goes to stool or takes a bath. Homans (10) emphasizes the importance of elevating the legs in established thrombosis in order to prevent the growth of the fragile clot (which a slow stream encourages) by the hurrying of a collateral stream past the proximal end of the thrombus. He says there is no reason why the leg should not be elevated and no reason against its being moved, the proximal end of the thrombus being within the pelvis and little influenced by such factors. The occurrence of pulmonary infarction should lead to a search for its source in order to determine whether a vein can be divided proximal to the process, protecting the patient from further and perhaps fatal embolism.

The use of heparin may prove to be the most significant discovery yet made in regard to preventing thrombosis and pulmonary embolism. Heparin was discovered in 1918 by Howell (45) who showed it to be an anti-coagulant. It was then considered not sufficiently pure to be utilized without complicating reactions. In Howell's experiments it was found to subsequently shorten the time of coagulation, probably also due to the impurity of the preparation.

Mason (46) in 1924 used tissue extracts to promote intra-vascular coagulation in rabbits. He found that purified heparo-phosphated neutralized the coagulation action of such extract and concludes that if clinical thrombosis and embolism are comparable

with experimental thrombosis and embolism the anticoagulant

offering so effective protection in one should be of use in the

other.

Shionaija (47) also studied the effects of the anti-

coagulants, heparin and hirudin, on extracorporeal thrombosis by

means of the extracorporeal vascular loop. In spite of adequate

single doses of the anti-coagulants white thrombi were formed

and obstruction to the flow eventually followed but the forma-

tion of red thrombi was markedly retarded. He found that the

structure of white thrombi formed after the use of anti-

coagulants was almost identical with those described by Welch

except that formation of fibrin was postponed and retarded.

Therefore, platelets were deposited in greater amount.

However, Shionaija's results were contradicted by Murray

and Best (48) and their co-workers in Canada who have done most

of the work on the use of heparin to prevent thrombosis. Using

a purified preparation of heparin injected intravenously, they

found that it prevented the formation of white thrombi in animals.

Microscopic study showed only a few red cells, white cells and

platelets but no characteristic thrombus where heparin was used.

Where heparin was not used, typical white thrombi were formed.

In a more extensive series of experiments Murray and

Best (49) injured the veins of dogs by mechanical and chemical

means. They found that the incidence of obstruction of peri-

pheral veins of dogs by thrombi formed as a result of this

injury is definitely decreased when a solution of purified heparin was given before and for prolonged periods after injury. They also found that the clotting time of blood of the normal human may be increased by intra-venous heparin. No deleterious effects were noted in five days of injection. At this time the authors suggested that clinical research should proceed along the following lines.

1. Attempt to determine cases likely to thrombose.

2. Administration of heparin postoperatively to these cases.

3. Use of heparin in cases of recurrent thrombosis and after embolectomy.

Crafoord (50) was the first to report the results of using heparin postoperatively to prevent thrombosis. He used it in 12 cases intravenously, prolonging the coagulation time considerably. The effect differed from that in normal man; a larger quantity being required to produce the same effect for about the next 24 hours after operation. There were no toxic effects. Because of the tendency to bleeding with heparin, Crafoord thought it should not be given until more than three hours postoperatively. There were no pulmonary emboli in this series which of course was too small to draw any definite conclusions.

Murray and Best (51) in 1938 wisely suggested that the use of heparin should be restricted to clinics where all facilities

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necessary for study are available and where accurate records of
the incidence of postoperative thrombosis have been kept. The
method they use is to add heparin in intravenous saline drip
(10 mg./100 cc.) at a rate to give a clotting time of 15 minutes
(2-3 times normal) determined by capillary tubes. This can be con-
tinued up to 14 days after operation and is being used after ex-
tensive surgical operations by the authors. Careful hemostasis
should be practiced at operation because of the increased ten-
dency to bleeding.

Murray (52) has very recently reported on 440 hospital
patients treated with heparin. Thrombosis and embolism did not
occur in any of these patients. Heparin was also used to treat
patients with thrombophlebitis and they were thought to be im-
proved. Striking improvement was observed in a group of 29
patients with pulmonary embolism. None had further embolisms and
none died of pulmonary embolism. These patients were treated a
few hours to several days after the attack. Murray suggests that
heparin is of benefit in these cases by preventing extension of
the embolus or thrombus.

Surgical Treatment

Kiser (53) gives the following brief history of the
surgical treatment of pulmonary embolism.

"The first interest in pulmonary embolus as a surgical
problem was by Trendelenberg who noticed that patients with pul-

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monary embolism did not die suddenly but might live 15 minutes
or longer. He first worked out the technic on cadavers and in
1907 reported an unsuccessful trial, attempting to remove the
embolus by suction. In 1908, Trendelenberg recommended the use
of special forceps and an arterial clamp rather than suction.
He used a rubber tube to constrict the pulmonary artery and aorta
during the operation. From 1908 to 1923 there were 20 failures
with the original method until Kuschner, one of Trendelenberg's
pupils, reported a successful case in 1924. A. W. Meyer modified
and improved the Trendelenberg operation by (1) an extrapleural
approach and pleural reflection; (2) the use of a smaller sound
and artery clip; (3) cutting down the strangulation time of 45
seconds by digital compression of the slit in the pulmonary
artery after shorter intervals of work. In 1935 a total of 51
surgeons, all but one of whom worked in European clinics, had
performed the Trendelenberg operation 132 times with 19 patients
surviving the operation and 9 cures. Only 25 operations were
done before Meyer had modified the technic. Meyer in 1932 had 4
successes out of 16 cases." Nystrom (54) and Crafoord (55) have
each reported 2 successful cases. The American surgeon Cutler
(56) in 1933 reported 4 unsuccessful cases. It is probable that
in an operation associated with such a high mortality, a large
number of the unsuccessful cases are not reported.

Very detailed and interesting descriptions of the opera-
tion can be found in articles by Nystrom (54) and Meyer (57). A

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serious handicap is the short period of time during which the
large vessels, the pulmonary artery and aorta, can be occluded
during the operation without seriously endangering the life of
the patient. Kiser (53) on the basis of experimental work in
dogs has suggested a method of constriction of the great vessels
whereby obstruction is placed on the afferent rather than on the
efferent side of the heart. He suggests that this method of
constriction lessens the likelihood of respiratory failure by
promoting cerebral stasis and protects the cardiac conduction
mechanism from damages of cardiac distention. By this method
the time of constriction was prolonged to $2\frac{1}{2}$ minutes in normal
dogs. Nystrom and Blalock (58) found that resumption of heart
beats and respiration may take place in the dog after occlusion
of the pulmonary artery and aorta for 6 minutes and 15 seconds.
The best results were obtained in experiments in which the pul-
monary artery alone was occluded, since recovery occured in 11
of 13 animals after occlusion periods of 5 to 12 minutes.

The Trendelenberg operation cannot be used except in
hospitals where immediate operation can be performed and perfect
surgical teamwork obtained. Even then the mortality is extremely
high. According to Gibbons (5) no successful cases in this
country had been reported by 1939. Other difficulties are the
fact that in many cases death comes before operation could be
performed, and in those that do survive a slightly longer period
it is difficult to know when to operate and when not. In Russum

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and Kemp's (25) series of 24 cases of fatal pulmonary embolism
15 patients died suddenly while the remaining 9 lived 8 minutes
to 24 hours allowing time for embolectomy if conditions had been
favorable. Meyer (57) who has had the most success with the
operation believes it should be performed where possible since
there is no sure means of avoiding embolism. He states, "It is
said that it is very difficult to know when to operate and when
not. One who has closely studied patients with this sickness and
who has closely followed the effects of treatment, devoting him-
self whole-heartedly to the work, giving of his time and patience,
such a man finds it easy to know when to operate. The patient
simply begins to die! And when the man of real experience sees
that the patient is dying, he knows that it is right and proper
to operate for embolism of the lung." However, because of the
great difficulties in the way of its successful performance, it
is probable that the operation will never be very universally
used. A more promising field is offered by treatment designed to
prevent thrombosis and embolism.

Medical Treatment

The various types of medical treatment advocated for
an established pulmonary embolus are difficult to evaluate. Since
even some apparently hopeless cases go on to complete recovery,
it is obviously impossible to draw conclusions from the use of the
treatment in only a few cases. Church (11) in 1892 described the

treatment used in a case of pulmonary embolism. "Dry cupping glasses and large poultices were applied freely to the chest and sides. Stimulants, whiskey, brandy and ammonia were given along with frequent hypos of sulfuric ether." The patient died. Church suggested using oxygen inhalation in these cases.

The use of oxygen is also advocated by Strong (59) and Gibbon (5) while White (21) suggests giving digitalis to help in supporting the right heart, and venesection to relieve distention of the veins. Recently papaverine has been enthusiastically recommended for treatment of pulmonary embolism by Collins (2). Its use is based on the concept of pulmonary embolism as owing its harmful effect chiefly to reflex spasm of the pulmonary arteries. In 1935 Allen and Maclean (60) reported a case of peripheral embolism relieved by the vaso-dilating action of papaverine intravenously and suggested its use in pulmonary embolism. These authors believe that the spasm is transient but that ischemia injures the intima of arteries and veins so that when the spasm abates widespread thrombosis occurs. De Takats (61) in 1936 reported the successful treatment of a case of pulmonary embolism using $\frac{1}{2}$ grain of papaverine intravenously. Collins (62) in 1938 reported the results of using papaverine in 17 cases of severe postoperative pulmonary embolism with only two deaths. This is an unusually large number of cases of postoperative pulmonary embolism to have been seen by one surgeon. However, Gibbon (5) objects to the use of vasodilating drugs such as papaverine, since

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the patient is already in a state of shock. Wright (63) who has recently studied the effectiveness of papaverine as a vaso-dilator claims that it is ineffective and uncertain in action. At the present time, the effectiveness of papaverine in the treatment of pulmonary embolism has not been proven, but on theoretical and experimental considerations it can hardly be expected to work any miracles.

Barnes (3) suggests combining the above mentioned methods of therapy as follows: If premonitory symptoms develop, have papaverine ready and make preparations for a Trendelenberg operation. In an attack give papaverine, morphine, oxygen and place the patient in a semi-upright position. Venesection should be done for marked cyanosis and digitalis given for subsequent cardiac embarrassment. If these methods fail, a Trendelenberg operation should be done. Collins (2) has offered the interesting suggestion that if the Trendelenberg embolectomy is necessary, the distal inferior vena cava caudad to the renal veins should be ligated to prevent subsequent fatal pulmonary embolism.

SUMMARY

In summarizing the points brought out by this paper,
the following observations seem worthy of emphasis.

1. Postoperative pulmonary embolism causes 6 to 8
per cent of all surgical deaths and is not an infrequent compli-
cation of medical conditions.

2. Although the pathology of thrombosis and subsequent
embolism is well understood, the fundamental cause of the thrombus
formation is not known.

3. In medical patients, cardiovascular weakness seems
to be an important factor predisposing to the formation of emboli
while in surgical patients, venous stasis, trauma and age are
probably of the most importance. Obesity, dehydration, infection
and operation in the abdomen and pelvis are other factors to be
considered. However, the fundamental cause in both medical and
surgical patients is probably some change within the blood itself.

4. Attempts to cut down the incidence of pulmonary
embolism by controlling the above mentioned predisposing factors
have been disappointing in their results. Nevertheless, in the
absence of any definite known cause for thrombosis and embolism
these attempts should be continued.

5. The use of heparin to prevent intra-vascular coagula-
tion seems, on the basis of experimental work, to offer the most
hope for the effective prevention of thrombosis and pulmonary

emboli. Unfortunately, it has not been used clinically long enough to draw any definite conclusions. It also has the disadvantage, at present, of being very expensive.

6. The symptoms of pulmonary embolism may be confused with coronary thrombosis in which case an EKG is of definite value.

7. Experimental work on animals indicates that the effects of a pulmonary embolus are due primarily to its acting as a mechanical plug rather than to any reflex effects. The use of the vasodilator, papaverine, is based on the theory that the harmful effects of pulmonary emboli are due primarily to reflex spasm of the pulmonary arteries. Therefore, this drug, which is fairly popular at present for the treatment of pulmonary embolism, should be of little value. The use of this vasodilator may even endanger the life of the patient who is already in a state of shock.

8. Supportive treatment including oxygen, morphine and perhaps digitalis is indicated in an attack of pulmonary embolism.

9. Although theoretically a life saving measure, the Trendelenberg operation has too limited an application to ever be of much value in the treatment of pulmonary embolism. It can only be performed under ideal conditions and even then carries a terrific mortality.

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