Physiologic and Histologic Changes in the Lungs of Patients Dying after Prolonged Cardiopulmonary Bypass:

An Inquiry into the Nature of Post-perfusion Lung

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ONE OF THE consistent postoperative complications of open cardiac operations with extracorporeal circulation is continuing and sometimes irreversible pulmonary insufficiency. Although the repaired heart may function well throughout the immediate postoperative period, pulmonary damage or dysfunction often adds morbidity or mortality to an otherwise well-conceived and executed open-heart procedure. Various histologic changes have been noted in the lung following bypass, but questions still remain as to their precise nature and etiology.

The lungs of patients dying early after prolonged cardiopulmonary bypass have been studied functionally before death and pathologically following death to correlate the findings and further elucidate the problem of the postperfusion lung syndrome. As many pulmonary changes occur rapidly following extracorporeal circulation, rigid criteria were proposed for selection of patients to demonstrate maximum physiologic and histologic effects attributable to the operative procedure early in the postoperative period.

Materials and Methods

From those patients undergoing open-heart surgery between 1963 and 1965 at the Peter Bent Brigham Hospital, 18 were included who had undergone prolonged pump runs and who had died within 3 days of operation. By the biased nature of the series, acute alterations associated with the operative procedure could be separated from the more chronic pulmonary changes of long standing cardiac insufficiency. No effort was made to differentiate between patients with diseases of the aortic and mitral valves or to assess risk, as most of these patients had compromised pulmonary function preoperatively, and others in whom function was comparable to this group recovered following operation. Table 1 lists the age and sex of the patients and operative procedures. More patients dying with aortic valvular involvement fit the criteria of the study than did those with mitral disease. The former often succumb more acutely from cardiac arrhythmias while those with mitral valve replacements may live for several days after operation, ultimately to die with progressive cardiac failure.

The duration of bypass is indicated in Table 2. The prolonged times on cardiopulmonary bypass were due to technical aspects of the procedure in seven cases. Intractable arrhythmia or arrest, or inability to sustain cardiac action off bypass prolonged perfusion times in 11 patients. One of the patients underwent 2 hours of veno-venous bypass following the original 2-hour pump time because of persistent inability

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TABLE 1.

Patient	Age & Sex	Procedure	Ventilatory Function: Vital Capacity (% predicted)	Ventilatory Function: Max. Breathing Capacity (% predicted)	Pulmonary Vasc. Resistance (dyne sec cm^{-5})
K. M.	57 M	AVR + pacemaker	80	68	425
E. N.	54 M	AVR	90	93	240
R. F.	41 M	AVR + pacemaker	66	51	155
J. L.	18 M	AVR	85	48	normal
J. B.	51 F	AVR	64	73	normal
F. deF.	50 F	AVR	70	148	—
J. E.	48 F	AVR	83	140	310
L. C.	58 F	AVR + pacemaker	61	92	300
N. C.	35 F	AVR	55	87	830
P. H.	59 M	AVR + pacemaker	66	44	—
W. N.	64 M	Open mitral valvuloplasty with Ivalon leaflet	69	67	350
D. P.	38 F	MVR	60	50	400
L. E.	31 F	MVR	37	64	1050
B. M.	38 F	MVR + aortic + tricuspid FX	71	53	215
R. C.	40 M	MVR + closure of ASD	63	40	240
T. E.	41 F	MVR + AVR	70	80	275
J. F.	30 M	MVR + AVR	55	87	130
P. H.	53 F	MVR + AVR	90	89	540

to sustain oxygenation. Another patient had both aortic and mitral valves replaced with 3 hours of bypass. Eighteen hours following operation, she had veno-arterial bypass plus hemodialysis because of intractable hypotension and renal shutdown. All patients died within 72 hours of operation; the majority (14/18) dying within 24 hours.

In all patients four units of cross-matched ACD blood (not older than 4 days) were used to prime the pump following dilution with a mixture of 2,000 cc. Ringer's lactate solution, 60 mg. Heparin, 2 Gm. Staphcillin, 100 Gm. albumin, 12.5 Gm. mannitol, 1 Gm. calcium chloride, 44 mEq. sodium bicarbonate, and 50 cc. 50% dextrose. This produced a hematocrit in the priming mixture of approximately 20%.

TABLE 2.

Duration of Bypass	No. Pts.	Time of Death	No. Pts.
2–3 (hrs.)	4	Intra-op	3
3–4	7	0–12 (hrs.)	4
4–5	2	12–24	7
5–6	1	24–48	1
6–7	4	48–72	3

Clinical records, laboratory data, autopsy protocols and gross pathology reports were reviewed. Tissues for microscopic examination were fixed in 10% buffered formalin. All sections were stained with hematoxylin and eosin, periodic acid-Schiff, and Verhoeff's elastic tissue stain. Formalin fixed tissue was cut on a cryostat and stained for fat using Sudan IV.

Results

Physiologic alterations. In the preoperative evaluation of pulmonary function, all patients had at least moderate reduction of ventilatory values (Table 1). All but two patients having cardiac catheterization showed pulmonary hypertension of significant degree, with pulmonary vascular resistance calculated between 150 and 1,050 dyne sec. $cm.^{-5}$ (normal value = 100 dyne sec. $cm.^{-5}$). Oxygenation of patients was closely monitored by serial arterial blood determinations postoperatively. All patients remained intubated and

on controlled respiration throughout their entire postoperative courses, except one who underwent tracheostomy an hour before death, and one who breathed an oxygen-enriched atmosphere spontaneously by natural airway for 2 hours before death.

Inspiratory and arterial oxygen tensions were compared and followed throughout progressively downhill postoperative courses. A common denominator was the onset and increase of pulmonary insufficiency and hypoxia in the face of adequate ventilation and oxygenation. Arterial oxygen tensions could be maintained at high values initially but commonly fell to low levels at 20–24 hours despite inspired oxygen concentrations between 40–100%. This non-specific course of events is not uncommon and has been recently documented again by Lyons and Moore in a detailed clinical study of critically ill surgical patients.[10] Chronic pulmonary disease, increasing cardiac failure and pulmonary shunting of blood by perfusion of non-ventilated segments were considered major reasons for this progressive hypoxia. Terminal events were generally precipitated by respiratory insufficiency, progressive hypercapnia, lactic acidosis and anoxia. The apparent ultimate causes of death are listed below:

Diagnosis	Number of Patients
Arrhythmia or asystole	11
Acute myocardial infarction	2
Intractable heart failure	2
Cerebral edema and herniation of cerebellar tonsils	1
Bleeding diathesis	1
Cerebral hemorrhage	1

Pathologic observations. Changes in the lungs of the 18 patients were reviewed. Although a consistent pattern of alterations was found, there were variations from patient to patient. The lungs at autopsy were increased in weight, averaging between 600 and 650 Gm. (normal 200–400 Gm.). Pleural surfaces generally showed minimal thickening and fresh fibrinous adhesions. Pulmonary arteriosclerosis was common. A few lungs contained recent pulmonary emboli with infarction. Lung parenchyma showed all gradations of congestion and collapse ranging from minimal changes to complete atelectasis. Bronchi and bronchioles frequently contained blood tinged mucous secretions. Frank pulmonary edema was present in several cases.

Microscopic changes were separated into those judged to be of long duration, and those of recent onset. The former consisted of an overall increase in fibrous connective tissue primarily in alveolar septae, and around blood vessels and bronchioles. Pulmonary vascular changes included intimal and medial fibrosis, atherosclerosis, and occasional organized emboli. Subpleural lymphatics were dilated in several lungs. A feature of virtually every lung was hemosiderin-laden macrophages in alveoli. These alterations have long been associated with chronic cardiac failure.[19]

Superimposed were changes of an acute nature. Vascular congestion was prominent with erythrocytes suffusing both pulmonary arteries and alveolar capillaries. Atelectasis, focal and diffuse, was consistently seen. Alveolar septae were hypercellular and thickened due to increased prominence of lining cells, mononuclear cells, an occasional polymorphonuclear leukocyte, and congestion of small vessels. Fresh hemorrhage and edema was commonly seen within alveoli and bronchioles and in one case hyaline membranes were prominent. A few lungs contained bone marrow, fibrin, and platelet emboli. The presence of fat was limited to small masses in three lungs. In a few small arteries of one lung there was acute arteritis with swelling and edema of both intima and media and accompanying infiltration of polymorphonuclear leukocytes. Acute broncho-pneumonia was observed in one patient (Figs. 1–5).

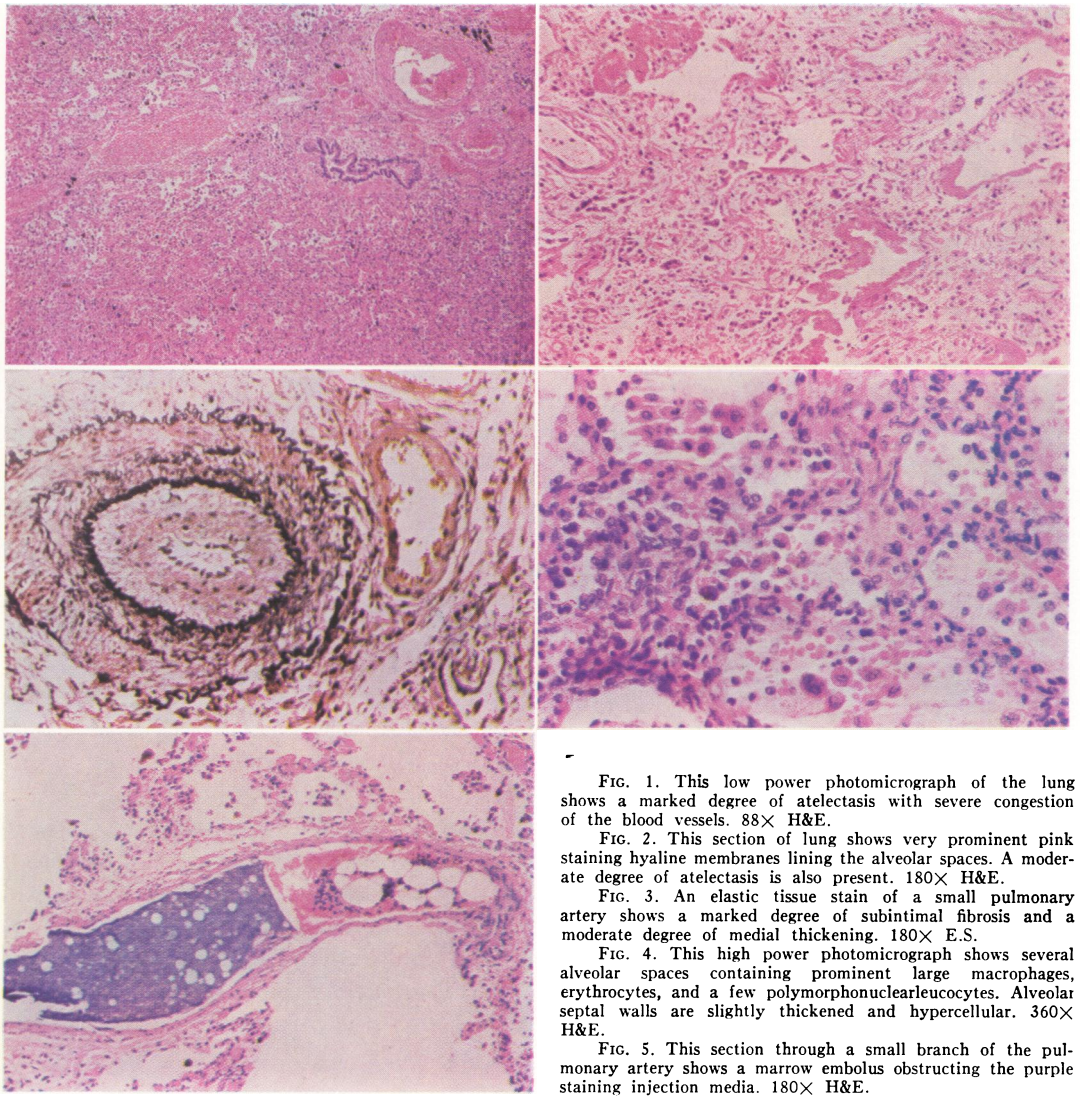

FIG. 1. This low power photomicrograph of the lung shows a marked degree of atelectasis with severe congestion of the blood vessels. 88× H&E.

FIG. 2. This section of lung shows very prominent pink staining hyaline membranes lining the alveolar spaces. A moderate degree of atelectasis is also present. 180× H&E.

FIG. 3. An elastic tissue stain of a small pulmonary artery shows a marked degree of subintimal fibrosis and a moderate degree of medial thickening. 180× E.S.

FIG. 4. This high power photomicrograph shows several alveolar spaces containing prominent large macrophages, erythrocytes, and a few polymorphonuclearleucocytes. Alveolar septal walls are slightly thickened and hypercellular. 360× H&E.

FIG. 5. This section through a small branch of the pulmonary artery shows a marrow embolus obstructing the purple staining injection media. 180× H&E.

Discussion

Many patients develop a gradual and diminishing ability to oxygenate their blood following open-heart surgery. They are weaned from the respirator while progressive respiratory insufficiency is developing. Removal from the respirator may become impossible as lungs lose compliance, and the patients eventually die with hypoxia. The nature and etiology of the pulmonary changes have been the subject of numerous studies since the first description by Dodrill in 1958.[3] The syndrome of post-perfusion pulmonary collapse was characterized as a diffuse and non-segmental atelectasis, typically not appearing on chest roentgenograms. Microscopically, spotty alveolar and perivascular hemorrhage was seen in conjunction with marked congestion of small vessels.

These changes of pulmonary atelectasis,

TABLE 3. *Postulated Etiologies of the Post-perfusion Lung Syndrome*

I. Mechanics of Operation
bilateral thoracotomy
right ventriculotomy
excess coronary suction
various types of oxygenators
ethylene oxide sterilization of pump tubing
length of procedure
prolonged hypotension
prolonged anoxia
II. Overloading of the Pulmonary Vascular Bed
inadequate left atrial drainage
mycardial failure
homologous blood syndrome
III. Hypothermia
IV. Perfusion and Perfusate
blood trauma
blood incompatibilities
hemoconcentration and sludging
denaturation of plasma proteins
vasoactive substances
V. Emboli
red cell
platelet
fibrin
fat
silicone
air

congestion, and hemorrhage must be considered non-specific, however, as similar lesions have been found in the lungs of patients in shock and hypoxia from various causes, as well as in experimental animals subjected to these conditions.[12] In early experiments, homologous dog lungs were used in conjunction with a mechanical pump as a means of extracorporeal oxygenation. The histologic alterations in these lungs also differed little from the changes initially described by Dodrill.[17, 21] The importance of pulmonary arteriovenous shunting such as occurs with perfusion of nonventilated alveoli in atelectasis has been emphasized. Such effects are commonly seen in association with valvular heart disease and are manifested by a progressive reduction in arterial oxygen tension despite increasing tension in the inspired air.[5, 11, 16]

An early explanation for the appreciable pulmonary congestion was inadequate venting of the bronchial artery inflow into the left atrium.[13] This possibility has been recognized and corrected. Table 3 lists other postulated etiologies, many of which have been subsequently dismissed. Another explanation of pulmonary congestion has been proposed by Litwak,[9] who suggests that plasma and red cells are sequestered in the lungs and splanchic bed and must be replaced to maintain normovolemia. Later when the sequestered blood is mobilized, massive overloading of the circulation occurs.

The effect of hypothermia in conjunction with cardiopulmonary bypass has been considered by some to cause atelectasis and intravascular aggregation of erythrocytes.[1, 4] All patients in this series were gradually cooled to 26° C., which was considered a satisfactory level for the regulation of metabolism, control of the myocardium, the protection of the perfusate and pulmonary circuit during bypass.

Much attention has been given to the nature of the perfusate in cardiopulmonary bypass. Hemodilution of the perfusate is now widely used as dilution is considered to reduce blood viscosity, increase perfusion of the capillary bed, and decrease aggregation of red cells.[6] It has been observed that plasma proteins are denatured at the blood-gas interface of most oxygenators. Lee[8] has shown that globular protein molecules unfold into long-chain macromolecules upon the interface, with subsequent precipitation and flocculation. With these protein alterations, vascular stasis and hemagglutination in the capillaries of the lung and other organs have been described. At the same time, fat emboli may be released by fracture, by the fragmentation of the protein capsules of chylomicra

with aggregation and formation of fat globules or by re-esterification of free fatty acids from plasma. Fat emboli may also result from either operative division of sternum and ribs or the trauma of resuscitation. In these cases the pump perfusate was quite dilute (Hct. 20%); few red cells, platelets, fibrin or fat emboli were found in the lungs examined.

Another factor that has been implicated is damage to cellular elements of the blood during perfusion. Neville[15, 18] took serial lung biopsies both during and after bypass and reported large numbers of polymorphonuclear leukocytes crowding arterioles and alveolar capillaries, with intimal margination and intramural migration in the larger vessels. This cellular response is thought to occur against perfused red cells which may release a leukotoxic substance which promotes this effect. It is thought that these changes are due to hemolysis of mixed bloods since no such alterations are observed if carefully cross-matched donor blood or autologous blood is used, or after closed cardiac operations. An increase in plasma hemoglobin levels corresponding to the increase in perfusion time has been found in our patients. An intense leukocyte response in the lungs, however, was not observed.

Still another facet of this problem may be immunologic as proposed by Schrenk and Neville.[18] They suggest that lymphocytes and neutrophils in mixed bloods of genetically unrelated donors react as antigen and antibody and result in damage to these leukocytes. Some of the functional and histologic changes observed in the post-perfusion lung thus is due to the presence of these altered cells.

In contrast, Nahas *et al.*,[14] noted pyronine-positive cells in the intraalveolar and perivascular spaces of dog lungs perfused with homologous blood. The similarity of these cells to those observed infiltrating homografted organs supports the concept of a graft versus host response, the fresh leucocytes in the perfused homologous blood reacting against the pulmonary tissue.

Mature plasma cells were not prominent in the lungs studied in this series, although immature forms with pyroniniphilic cytoplasm could not be excluded. Assuming their presence, the question remains of their role in the post-perfusion lung. The production of antibodies against components in the perfusate would seem to require a significant interval of time, during which the pulmonary changes would have already occurred. An immune reaction has yet to be demonstrated.

Vasoactive substances, serotonin and histamine, released by injured platelets and leukocytes have been shown to cause severe bronchoconstriction and may contribute to the pathologic changes in the post-perfusion lung[7]; serotonin has also been shown to have a strong vasoconstrictive effect on small pulmonary arteries,[2] producing pulmonary hypertension.

In the evaluation of different factors contributing to pulmonary dysfunction following open-heart operations, several features seem to dominate. Chronic pulmonary damage secondary to the original cardiac disease needs emphasis. Superimposed upon this are the pulmonary changes associated with prolonged general anesthesia, the accumulation of secretions within bronchi which contribute to atelectasis. Alterations of blood elements during the bypass procedure must occur, but no effects were recognized in this study which could be related definitely to this change. The most striking factor found was progressive cardiac decompensation following operation with terminal pulmonary edema or cardiac arrhythmia. Vascular congestion, lymphatic dilatation, pulmonary edema and hemorrhage are alterations long recog-

nized as associated with acute heart failure. These factors acting in concert provide a reasonable, if incomplete, explanation for the clinical and pathologic features that characterize the post-perfusion lung. Future studies on pulmonary surfactant, immunochemistry, and other aspects of this problem may provide a more sophisticated understanding of these changes.

When considered in this framework, the "post-perfusion lung" hardly appears to be a single or unique syndrome but is rather a variable end-result from the interplay of many causative factors.

Summary

In an attempt to lend better definition to the problem of the post-perfusion lung syndrome, the lungs of 18 patients dying within 72 hours after prolonged cardiopulmonary bypass have been examined clinically and pathologically.

Each patient had chronic pulmonary disease and most had significant pulmonary hypertension documented prior to their open heart surgery. Postoperatively, all demonstrated progressive respiratory insufficiency and hypoxia, despite high ventilatory oxygen tensions.

The lung pathology was differentiated into the chronic changes of long term cardiac insufficiency, and those of an acute nature. The many factors thought to contribute to this syndrome are reviewed. It should be emphasized that the pulmonary alterations of perfusion are of a non-specific nature and similar to changes seen with other forms of acute progressive postoperative pulmonary insufficiency.

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