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A REVIEW OF FOUR DREADED COMPLICATIONS OF OPEN-HEART OPERATIONS

CAUSES, AVOIDANCE, AND TREATMENT OF ACIDOSIS, OVEROXYGENATION, HEART-BLOCK,
AND PULMONARY DAMAGE

BY

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Open-heart operations using total-body perfusion may be accompanied by complications that do not commonly occur in other types of thoracic surgery. This is a review of the most important complications: metabolic acidosis (Ito *et al.*, 1957), overoxygenation (Ito *et al.*, 1958), heart-block (Olmsted *et al.*, 1958a) and pulmonary capillary damage (Kolff *et al.*, 1958). Each has been discussed in separate papers with exhaustive documentation, analysis, and bibliography.

The clinical analysis to be presented is based upon findings in 150 consecutive patients who underwent open-heart operations in the hospital of the Cleveland Clinic Foundation. The types of heart-lung machines used were the membrane oxygenator (Kolff *et al.*, 1956), the Melrose (1955) oxygenator, the Björk oxygenator (Kolff *et al.*, 1957), and the modification of the Björk oxygenator as described by Kay *et al.* (1956)¹ in combination with "sigmamotor" pumps or non-occlusive roller pumps of our own design.² In 75% of our patients the heart was stopped with potassium citrate according to Melrose's technique as previously described (Kolff *et al.*, 1957).

During the post-operative period radiographs of the chest were made. In each patient the first was made approximately three hours post-operatively; the second that night; and others during the days following if necessary.

Acidosis

Three or more hours after completion of an operation, when overventilation by the anaesthetist is no longer present, the pH of the blood occasionally falls to a level that is incompatible with life. Whatever the underlying cause, in these patients the mechanism of death seems to be an acidosis leading to respiratory failure followed by cardiac arrest.

Blood samples for the determination of pH and of CO₂ content were drawn from the inferior vena cava

through an indwelling polyethylene catheter. The pH of this caval blood may be expected to be a little lower and its CO₂ content somewhat higher than that of the corresponding arterial blood.

The acidosis appears to be caused not by damage to the blood by the pump-oxygenator during the period of by-pass, but rather by a period of inadequate total-body perfusion as evidenced by, for example, low arterial pressure. Indeed, experimentally the pH and the CO₂ content of the blood can be lowered simply by reducing the cardiac output. We reduced the cardiac output in anaesthetized dogs either by partially ligating the venae cavae or by obstructing them with rubber balloons attached to cardiac catheters (Ito *et al.*, 1957). In this way the arterial pressure was reduced to 40 mm. Hg. Two hours of reduced circulation lowered the blood pH to about 7, notwithstanding overventilation, so that both CO₂ content and pCO₂ were low; consequently this acidosis was not respiratory, but metabolic.

Our data on 35 consecutive patients treated with heart-lung machines conformed to the well-known fact that small children are more likely to develop acidosis than are adults. The lowest pH values occurred not during or immediately after, but three hours after the by-pass. Because of overventilation by the machine and by the anaesthetist, the CO₂ content for this group was lowest immediately after the by-pass and returned to a low normal value three hours later.

All patients had less than normal circulation (artificial cardiac output) during the by-pass, but, in order to detect any correlation that might exist between grossly inadequate circulation and acidosis, cases were listed according to the occurrence of "hypotension." Hypotension was regarded as being present if the mean arterial blood-pressure was less than 50 mm. Hg during extra-corporeal maintenance of the circulation, or if it was less than 60 mm. Hg during the pre-run or post-run phases. The average of the pH values in the group with hypotension was lower than that in the group without hypotension. The data support our thesis that metabolic acidosis after open-heart operation results from the

¹ Commercially available from Pemco Inc., 5663, Brecksville Road, Cleveland 31, Ohio.

² Presented to us and made by Mr. Laddie C. Hercik, of the Hill Acme Company, Cleveland, Ohio.

decreased circulation. The $p\text{CO}_2$ was not elevated, so that the acidosis must be metabolic rather than respiratory.

Since the low $p\text{H}$ and low CO_2 content follow decreased circulation, we expected the same phenomenon to occur in some patients not subjected to extracorporeal circulation, but it is rarely looked for at the proper time. Indeed, we found acidosis in other patients after periods of hypotension which followed a variety of operations. Thus to avoid the occurrence of acidosis every attempt is made to avoid periods of low perfusion as evidenced by low arterial pressure before, during, and after the by-pass. Notwithstanding these attempts, acidosis still occurs in patients when there is trouble, and especially in the very young. When a low $p\text{H}$ is found or expected a standard procedure is followed: commercial sodium bicarbonate solution,³ 4.5 mEq/kg. of body weight, is diluted with a double volume of 5% fructose in water, and started intravenously as a slow drip to be infused during the first six hours after operation. The blood $p\text{H}$ is determined three and six hours post-operatively; and if the downward trend is corrected the infusion is discontinued. However, if the $p\text{H}$ is still low six hours post-operatively and after completion of this dose of sodium bicarbonate, a second similar dose is started, to be administered during the next 12 hours. Sodium bicarbonate should not be given unless its need is definitely indicated, since it causes an increase of serum sodium content.

Overoxygenation

Exposure to oxygen under higher than atmospheric pressure does not occur in nature. Defence mechanisms of the organism to overoxygenation therefore cannot be reasonably expected. Our interest in preventing overoxygenation is based on our impression that it might be the cause of some sudden unexpected fatalities that occurred 10 to 12 hours after perfusion.

If a human being is exposed to a high pressure of oxygen, manifestations of oxygen intoxication rapidly appear. A common early symptom is twitching of the lips or the muscles of the arms; other symptoms are dizziness, nausea, vomiting, irregular respiration, confusion, and, in some instances, convulsions and unconsciousness (Muralt, 1954).

At atmospheric pressure, 90 to 95% of oxygen can be breathed by man for short periods without ill effects. Pichotka and Kuhn (1947) found that, in guinea-pigs and rabbits, death eventuates after continuous exposure for 75 hours.

The occurrence of retrolental fibroplasia in premature infants who have been maintained in an oxygen tent is a clear example of oxygen toxicity, notwithstanding that only the partial pressure of the oxygen was increased (Patz, 1955). In artificial oxygenators the partial pressure of oxygen can become much higher than that in the human lungs.

If pure oxygen is used in the oxygenator, overoxygenation of blood is likely to occur under the following conditions: (1) during circulation of blood through an oxygenator prior to connecting the patient to the machine; (2) during partial cardiac by-pass with a small flow rate, which is a routine procedure at the

beginning and at the end of many perfusions; and (3) during perfusion of a small patient with an oxygenator of large capacity.

Though oxygenation of blood by most heart-lung machines takes place under atmospheric pressure, the partial pressure of oxygen in the oxygenators can approach 700 mm. Hg if the blood is oxygenated with oxygen plus 1.5% of CO_2 at a barometric pressure of 760 mm. Hg and at a temperature of 37°C . (the water-vapour pressure would account for 47 mm. Hg and the 1.5% of CO_2 for 11 mm. Hg). The solubility of oxygen in blood decreases with a rise in temperature (Ito *et al.*, 1958). If, for example, the temperature of the blood is 30°C . in the oxygenator and it increases to 37°C . in the patient's body, the $p\text{O}_2$ would increase from 700 to about 800 mm. Hg (Penido *et al.*, 1957). That overoxygenation can do no harm is unlikely, and the burden of proof seems to lie upon those who refute the evidence that it does.

To avoid overoxygenation we use the Clark polarograph⁴ (Clark *et al.*, 1953). There is a linear relationship between polarographic readings and oxygen tension. On the other hand, oxygen content increases only slightly after the haemoglobin has been fully oxygenated. Thus, measurement of oxygen tension by a polarograph provides a better estimate of high oxygen values than does measurement of oxygen content or oxygen saturation.

Heart-block

Complete atrioventricular block cannot always be avoided during surgical repair of congenital malformations of the heart. It has caused many deaths, either directly after the operation or later. A-V block may be caused by surgical damage to the conductive system, but this may be reversible. It may also occur as a result of temporarily disturbed metabolism due to insufficient circulation, anoxia, potassium effect, or to other changes.

In some patients a sufficient increase in ventricular rate, notwithstanding heart-block, can be obtained with chronotropic drugs such as isoprenaline hydrochloride ("isuprel" hydrochloride; isoproterenol).⁵ However, the hearts of some patients are refractory to such drugs, or become so, and a satisfactory heart rate can be obtained only by electrical stimulation.

A pacemaker provides an electrical stimulus to the ventricles when it is necessary to increase ventricular rate (Zoll *et al.*, 1956; Allen and Lillehei, 1957; Burchell, 1957; Olmsted *et al.*, 1958a). If the stimulus is strong enough, the ventricles follow the pacemaker, provided its rhythm is faster than the intrinsic ventricular rhythm. In a patient having a heart-block with a ventricular rate of 40, any ventricular rate in excess of 40 can be imposed. A pacemaker will also work in atrial fibrillation with a slow ventricular response, and, of course, also in the few patients in whom there is no atrial activity.

One elegant pacemaker amplifies the sinus waves (P waves) with transistors and a hearing-aid battery (Folkman and Watkins, 1958). This amplified impulse is applied to the ventricles. Other pacemakers generate

³ Available in 50-ml. ampoules containing 44.6 mEq, from Abbott Laboratories, North Chicago, Ill.

⁴ Commercially available from Yellow Springs Instrument Company, Yellow Springs, Ohio.

⁵ Isuprel hydrochloride can be given intravenously, 0.1 to 0.5 mg., starting with 0.02 mg.; optimum dose is usually 0.04 mg. It can also be given intramuscularly or in the form of sublingual tablets (5 mg.) as often as needed.

their own rhythm. Zoll *et al.* (1956) has designed pacemakers for use with external electrodes. Kirklin (Burchell, 1957) uses that type of pacemaker with external electrodes to maintain the ventricular rate in patients having atrioventricular blocks after open-heart operations.

In many instances the heart will regain a normal sinus rhythm if the patient is maintained for a few days at an adequate ventricular rate. Even if a sinus rhythm is not restored, the heart may be given time to adjust to a low ventricular rate that is to be permanent.

When an atrioventricular block is recognized in a patient on the operating-table, even when the ventricular rate at that time is sufficient, we suture two electrodes⁶ against the ventricular myocardium and lead them out of the chest through separate puncture holes. Thus the pacemaker can be used at any time when the ventricular rate becomes low. The circuit of our pacemaker has been described by Olmsted,⁷ but commercially available pacemakers may be used. We believe that it is no longer justifiable to undertake open-heart surgery without a pacemaker at hand.

Pulmonary Complications

Pulmonary complications (Allen and Lillehei, 1957) were at one time a frequent cause of death in open-heart operations. However, with the recognition and elimination of many of the possible factors that lead to their development, pulmonary complications now are becoming rare.

Factors in the Occurrence of Pulmonary Complications After Open-heart Operations.—(1) Pulmonary complications occur twice as often in patients with pre-existing pulmonary vascular disease as in those without such disease. (2) It is believed that oxygen intoxication and exsiccation of the alveolar and capillary cells may follow the ventilation of the lungs by undiluted oxygen during the period of total by-pass when the lungs are not perfused with blood. We have followed the procedure of Kirklin (Patrick, 1957), who keeps the lungs gently inflated (without moving them) with a mixture of 50% helium and 50% oxygen. (3) Small children are especially likely to develop pulmonary complications because their bronchioles are small and are easily plugged with mucus or debris. Early tracheotomy may help. Postponement of open-heart operation until the child has reached the age of 2 years is recommended whenever possible. (4) Too much saline solution is present in some commercial blood-collecting bottles, and too much electrolyte or dextrose solution is sometimes given to keep the venous infusion going. (5) Air embolism originating from the right side of the heart can easily occur and does not seem to be so innocuous as was once thought. Slush (air bubbles and blood), even if it does not increase the resistance when flowing, causes a high resistance after temporary interruption of the flow (Kolff *et al.*, 1958). The forces necessary to get the slush moving again through the capillary bed may be larger than those available. (6) Temporary overloading of the pulmonary circulation with blood seems to us to be the most important single factor causing pulmonary damage.

⁶ Twenty-six gauge stainless-steel stranded wires, 15/1,000-in. (0.038-cm.) diameter, coated with "teflon," manufactured by Falls Hollow Staybolt Co., Cuyahoga Falls, Ohio.

⁷ Reprints showing circuit are available on request.

Evidence has been presented (Kolff *et al.*, 1958) which suggests that such overloading, even for short periods of time, may initiate capillary damage with various degrees of extravasation of blood. During the post-operative period these extravasations are increased by exudation and oedema until they seriously interfere with gaseous exchange.

A distressing ever-present x-ray finding is the increase in the pulmonary changes even when the cause of the initial damage has long since been eliminated. The pathological changes in the lungs in fatal cases usually include microscopic haemorrhages, oedema, fibrinous exudates, and, on occasion, fibrinous membranes covering or sealing the alveolar walls (Kolff *et al.*, 1958).

If the hypothesis is accepted that short periods of overloading of the pulmonary circulation can initiate capillary damage in the lungs and thereby initiate a sequence of serious events, every attempt should be made to avoid any overloading, however short its duration.

Sudden overloading of the pulmonary vascular bed with blood usually occurs by a combination of the following factors.

I. By forward overfilling:

- A. During partial by-pass if a sudden increase in the patient's blood-volume occurs.
- B. During total by-pass by accumulation of extravagant coronary sinus blood in the right heart.

II. Through collateral vessels:

- A. Open ductus.
- B. Increased bronchial circulation.

III. By retrograde overfilling:

- A. By mechanical factors:
 1. Obstruction of pulmonary vein.
 2. Mitral stenosis.
 3. Aortic and mitral regurgitation.
- B. Dynamic impediment (inability of the left ventricle to overcome the aortic pressure):
 1. Ventricular fibrillation.
 2. Ineffective left ventricular beat.

Forward Overfilling of the Pulmonary Vascular Bed

Overfilling by Volume Changes of the Machine During "Partial" By-pass.—Sudden decrease of the blood volume in the machine will lead to sudden increase of the patient's blood volume. This change may lead to a high venous pressure which may be passively transmitted to the pulmonary artery. Forward overfilling can be avoided by the following measures:

1. Rigid maintenance of a constant volume of the heart-lung machine will permit increase of the patient's blood volume only by intentional transfusion. The Gibbon type of oxygenator and the Clark and Gollan oxygenator (Helmsworth *et al.*, 1952) have an electrically controlled constant volume. Our Kay and Cross oxygenator (Kay *et al.*, 1956) has an electric automatic-control system (Olmsted, 1958b) that maintains the volume of the 21-in. (53-cm.) oxygenator within 150 ml. of blood.

2. Avoidance of irregularities in venous outflow. In some machines temporary difficulty with venous outflow may lead to negative pressures, which suck the walls of the venae cavae into the openings of the venous cannulae, blocking them and leading to changes in volume. This can be avoided by the use of a venous reservoir in which a slight (4 mm. Hg) negative pressure is automatically maintained (Jones *et al.*, 1955), or by the use of an open venous reservoir that can be moved up and down so that the degree of suction

can be regulated by the height of the siphon (Lillehei, 1957). We prefer the latter (Olmsted *et al.*, 1958b).

3. Monitoring of central venous pressure through a polyethylene tube introduced via the saphenous vein into the inferior vena cava reflects the patient's blood volume immediately. This tube stays in place, and is used for determinations of venous pressures and pH and blood transfusion during the first post-operative days.

Accumulation of Coronary Sinus Blood Can Occur Only When the Right Atrium is Closed.—A flow of coronary sinus blood may follow a period of anoxia of the myocardium, which occurs when the occluding clamp is removed from the base of the aorta after arrest by potassium citrate. This coronary flow after anoxia may amount to 50% of the total circulation (Maraist and Glenn, 1952). Opening of the vena cava usually suffices for draining the sinus blood out towards the venous cannula of the artificial heart; occasionally a cannula in the right atrium itself is necessary.

Filling of the Pulmonary Vascular Bed Through Collateral Vessels

An open ductus must be closed at the onset of extracorporeal circulation, as Dubbelman and Kolff found many years ago in very young calves (Kolff *et al.*, 1956). But if the residual pulmonary flow is small, closure before the machine is ready may cause difficulties in children. Increased bronchial circulation, as is often present in tetralogies, may lead to a large influx of blood into the lungs.

Convincing experimental proof of the importance of collateral bronchial circulation in the occurrence of pulmonary vascular overloading has been given by Muller *et al.* (1958). A cannula in the left atrium will drain off the excess blood.

Retrograde Overfilling, Mechanical (Obstruction or Insufficient Valves) or Dynamic (Insufficient Left Ventricular Contraction or Fibrillation)

Dynamic impediment to the outflow of the lungs is often overlooked. This impediment may occur when

Safeguard against overfilling of the pulmonary vascular bed: cannula in left atrium. This cannula is connected to a saline- or blood-filled manometer indicating the pressure in the left atrium. The cannula is also used to drain blood from the left atrium into the venous reservoir of the artificial heart. Overfilling of the pulmonary vascular bed thus becomes impossible.

there is ventricular fibrillation or an ineffective left ventricular beat. When the patient is returned to his own circulation the right ventricle may have developed a more effective beat against the pulmonary arterial pressure than has the left ventricle against the higher pressure in the aorta; high pressures measured by us in the left atrium indicate that this may occur during the first eight minutes after arrest with potassium citrate.

A large cannula in the left atrium (see Fig.) can prevent retrograde overfilling except when there is obstruction of a pulmonary vein. A simple saline- or blood-filled manometer connected to the cannula will indicate the pressure in the left atrium. We found that the pressure in the left atrium may build up in a matter of seconds to reach 50 cm. of saline or more. If a connexion is opened to the venous reservoir which is under the level of the heart, a constant flow of bright-red blood may be observed. **Warning:** No negative pressure should be applied to the cannula if there is an open connexion of the left atrium to the atmosphere, lest air be sucked into the heart cavities.

Once the pulmonary capillaries have been damaged and the patient is in pulmonary distress, the use of a positive-pressure respirator may be life-saving.*

Summary

Clinical observations on 150 consecutive patients who underwent open-heart operations were corroborated by laboratory experiments. The conclusions derived were later confirmed in the open-heart operations in 330 consecutive patients.

1. *Acidosis* is most severe three or more hours after operation. It may be expected not only after open-heart operations but also after other operations, whenever a low cardiac output as evidenced by low blood-pressure has been present for a considerable time. The younger the patient the more likely it is to occur. Acidosis mainly occurs when there has been trouble, and, if severe, may lead to death unless it is controlled by intravenous infusion of sodium bicarbonate.

2. *Overoxygenation* does not occur in nature, and it is unlikely that the human organism has a defence mechanism against it, though it has not been proved to have a deleterious effect.

3. *Heart-block* can occur after operations in the neighbourhood of the A-V bundle. It is no longer justifiable to undertake an open-heart operation without a pacemaker at hand. Whenever heart-block occurs, one electrode is sewn to the myocardium before the chest is closed, even though the heart-rate while the patient is on the operating table is still satisfactory.

4. *Pulmonary complications* in open-heart operations can nearly always be avoided. The most important single measure to prevent pulmonary complications is the use of a wide cannula in the left atrium, to measure the pressure in the left atrium, and to drain out blood into the pump oxygenator if this pressure proves to be too high. Pulmonary damage during open-heart operations is usually due to temporary overfilling of the pulmonary vascular bed with blood, leading to capillary damage. The conditions under which this may occur can be predicted. Dynamic insufficiency of the left

* The Bennett Respirator (V. Ray Bennett and Associates, Inc., Los Angeles 48, California) provides positive pressure during inspiration only. It is best applied via a cuffed tracheotomy tube.

ventricle is perhaps the most frequent cause. Increased bronchial flow in tetralogies and open ductus are other causes.

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INFLUENCE OF THE PITUITARY ON THE ERYTHROPOIETIC PRINCIPLE PRODUCED IN THE KIDNEY

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This study is a continuation of a previous work (Osnes, 1959). The purpose of this report is to demonstrate the stimulating influence of the pituitary on the erythropoietic principle produced in the kidney (K.F.=kidney factor).

It is well accepted that an anaemia develops after hypophysectomy, but opinions differ regarding the mechanism of post-hypophysectomy anaemia.

Flaks *et al.* (1937, 1938) reported that the oral administration of anterior lobe of ox pituitary or extracts of anterior lobe resulted in a significantly increased erythrocyte count in both normal and hypophysectomized rats, and postulated that the anterior lobe of the pituitary contains a specific erythropoietic hormone with the bone-marrow as its target organ. Meyer *et al.* (1940) were unable to obtain the results reported by Flaks *et al.*

White and Dougherty (1945) stated that continued daily injection of pituitary adrenotrophic hormone into

mice resulted in an increase in haemoglobin and in red cells. They concluded that the adrenotrophic hormone, by means of its trophic influence on the adrenal cortex, maintains a physiological control over the number of circulating erythrocytes.

A number of papers which deal with the erythropoietic effect of pituitary extracts and hormones have been published from the Institute of Experimental Biology and the Donner Laboratory, University of California (Garcia *et al.*, 1951; Contopoulos *et al.*, 1953, 1954; Van Dyke *et al.*, 1954, 1957). These investigators reported that normal rats injected with 0.5 mg. of adrenocorticotrophic hormone twice a day for 34 days showed normal haematological values, whereas after 116 days four rats showed a red-cell volume and a haematocrit level above those of normal controls. Oral administration of sheep anterior pituitary repaired the anaemia in hypophysectomized rats, and in adrenalectomized rats brought a 20% increase in circulating red-cell volume above that of either normal or adrenalectomized controls. Hypophysectomized rats injected with "pituitary erythropoietic factor" showed marked increase in red-cell volume, haemoglobin, and haematocrit. "These values were not only brought back to normal but exceeded normal value."

Based on these and other findings, the above authors postulated the existence of a pituitary erythropoietic factor distinct from the well-known pituitary hormones and with the bone-marrow as its target organ. Some of these authors felt that there also was chemical evidence for such an opinion.

Simpson *et al.* (1959), however, presented a re-evaluation of the evidence for a pituitary erythropoietic hormone and stated: "... there is no satisfactory evidence for a pituitary erythropoietic factor distinct from the known pituitary hormones. The adrenocorticotrophic hormone is clearly instrumental in the regulation of red-cell volume, as is thyrotrophic hormone and possibly growth and gonadotrophic hormones. The relative importance and mechanism of action of the several factors remains to be determined."

Several investigators believe that anaemia which follows hypophysectomy does not indicate any specific deficit in erythropoiesis and have claimed that the loss of the pituitary influence on the adrenals, gonads, and especially on the thyroid may be responsible for the developing anaemia. Crafts (1949) reported that in hypophysectomized rats treated with thyroxine, combined with testosterone propionate and high-protein diet, the haematocrit and haemoglobin values were maintained at normal levels and the number of erythrocytes increased above the control level.

The method used in the present work was described earlier (Osnes, 1959). To indicate the variation between the observations, ± 1 standard deviation has been calculated, and plotted in the graphs.

Experimental Findings

Fig. 1 shows the reticulocyte and haemoglobin values in a group of hypophysectomized bled rats and in a group of normal bled rats. It is seen that the reticulocytosis in the hypophysectomized bled rats was only about half the value of that observed in the normal bled controls. Many of the reticulocytes seen in the