Studies in Oxygen Consumption During Extracorporeal Circulation with a Pump-Oxygenator *

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PREVIOUS STUDIES have revealed certain physiologic abnormalities in experimental animals and in patients operated upon with the aid of a heart lung machine at low flow rates; [1, 3, 5, 8] metabolic acidosis with increased lactic acid levels, impaired liver function, and low oxygen consumption during heart-lung bypass have been noted in particular. The last finding was of special interest because of the fundamental importance of this factor in the tolerance of the body to extracorporeal circulation.

An experimental study was carried out to determine the rate of oxygen consumption during extracorporeal circulation using a pump-oxygenator and to evaluate the role of factors related to oxygen utilization, especially the rate of flow.

Methods

The oxygenator used in these experiments (Crafoord-Senning type) has been described in detail elsewhere.[5] In essence it consists of multiple, perforated, rotating cylinders which expose a thin film of blood to an oxygen atmosphere. In these experiments a sigmamotor pump, which could more conveniently be precalibrated to specific flow rates, was substituted for the standard pump of this machine.

Oxygen content was measured in arterial and mixed venous blood by the method of Van Slyke. Oxygen consumption during EC *** was calculated from the arteriovenous oxygen difference and the EC flow rate.

Oxygen consumption was measured spirographically before and after EC with an Elema "Metabograph." † After initial measurements with voluntary respiration the animals were maintained on artificial ventilation (positive-negative) with an AGA †† respirator arranged to function through the "Metabograph."

Cardiac output before and after EC and in control experiments was determined by the Fick principle on blood from pulmonary artery and femoral artery.

Arterial blood pressure was recorded from a U-tube mercury manometer connected to a femoral artery.

Temperatures were recorded rectally throughout each experiment. No appreciable changes in temperature occurred which could account for altered oxygen consumption. The extracorporeal circuit was warmed by infrared heat to avoid cooling of the blood.

Operative Procedure. Adult mongrel dogs weighing 11–22 Kg. were anesthetized with intraperitoneal Nembutal. Through a left thoracotomy incision cannulae were placed in the right atrium and left subclavian artery for venous return and arterial inflow during extracorporeal circulation. During the period of heart-lung bypass cardiac circulation was interrupted by

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*** For convenience EC is used in text and illustrations to indicate "extracorporeal circulation."

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tightening a sling-ligature around the pulmonary artery. Heparin, 4 mg./Kg., was administered intravenously before insertion of the cannulae. 30 mg. of heparin was added to each liter of donor blood used to fill the extracorporeal circuit.

Experimental Plan

The period from time of anesthetization until beginning heart-lung bypass was taken as the control period and data on oxygen consumption, blood pressure, blood oxygen saturation, and cardiac output referred to as "control" are those obtained during this period.

Relation of EC Flow Rate to Oxygen Consumption. Oxygen consumption was measured spirographically after induction of anesthesia. Additional doses of Nembutal, which could depress the metabolic rate, were never given after this point.

The EC flow rate was varied in step-wise fashion during the period of heart-lung bypass, in some cases progressing from high to low flow rates, in some cases from low to high flows, and in some cases alternating high and low flow rates. At each level the flow was held constant for 15 minutes and samples of arterial and venous blood were then taken from the appropriate connecting tubes (preliminary experiments indicated stabilization of oxygen consumption within ten to 12 minutes after changing the flow rate). Determinations were made at from three to five levels of flow in each dog.

For comparative purposes oxygen consumption was measured in a group of dogs at various levels of cardiac output. Oxygen uptake was determined spirometrically while reducing cardiac output in stepwise fashion by constriction of the pulmonary artery. Circulatory rate was determined at each level by the Fick principle, utilizing the spirometric record of oxygen consumption and the oxygen content of pulmonary artery and femoral artery blood samples. Determinations were made at intervals similar to those in the experiments with varied EC flow rate.

Effect of Elevating Arterial Pressure with Noradrenalin. EC was begun at a high flow rate and oxygen utilization determined. The flow rate was then reduced, held constant for 15 minutes, and blood samples again taken. Maintaining this same reduced flow rate, noradrenalin was given at a rate sufficient to elevate and maintain the blood pressure near control levels for 15 minutes and blood samples were again taken. After allowing a period for the effect of noradrenalin to subside the flow was further reduced and blood samples taken; noradrenalin was given again to raise the arterial pressure and blood samples taken. In this way the oxygen consumption (1) at high flow rate, (2) at reduced flow rates with consequently reduced blood pressure and (3) at reduced flow rates with artificially maintained blood pressure, could be compared.

Effect of Increasing EC Flow Rate with Simultaneous Decrease in Arterial Oxygen Saturation. For these experiments large animals were chosen and the number of rollers in the oxygenator was reduced below the figure known to be adequate for the size of the animal. This deficiency in oxygenating capacity allowed a high arterial oxygen saturation at low flows but resulted in a decreasing arterial saturation with higher flow rates. Flow was then varied in the same step-wise fashion as in the previous experiments and blood samples were taken at each level for calculation of oxygen consumption.

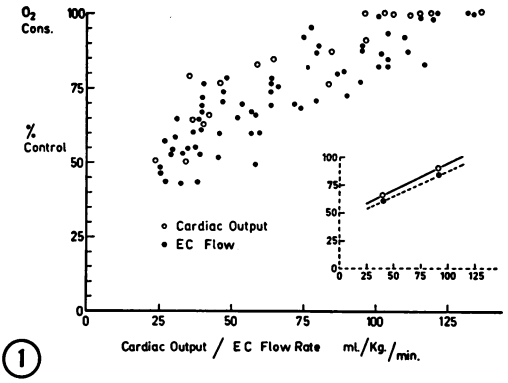
Results

Relation of EC Flow Rate to Oxygen Consumption. Since the individual basal oxygen consumption varied somewhat in different dogs (4.8–6.9 cc./Kg./min.), the spirographically determined oxygen uptake during the period from time of anesthetization until completion of thoracotomy was taken as "control" and oxygen consumption

calculated as per cent of control level. Mean arterial pressure decreased from a prethoracotomy average of 125 mm. Hg to an average of 90.5 mm. Hg after conclusion of all intrathoracic manipulations and placement of cannulae preparatory to beginning heart-lung bypass; cardiac output after completion of thoracotomy varied in different dogs from 100 to 125 ml./Kg./min., according to determinations by the Fick principle. Despite these changes, oxygen consumption remained constant in all dogs during the period from time of anesthetization to beginning of EC. In this group of 16 dogs oxygen consumption after EC was six to 12 per cent lower than control in two experiments, four to 15 per cent higher in four, and the same as control level in the remaining ten experiments.

Figure 1 illustrates the relation of flow rate to oxygen consumption in 16 dogs with 64 separate determinations. At flow rates ranging from 20 to 30 ml./Kg./min., average oxygen consumption was 52 per cent of control levels. As flow increased there was a progressive rise in oxygen utilization, approximating control values at perfusion rates above 100 ml./Kg./min.

Figure 1 also illustrates the relation of oxygen consumption to changes in cardiac output (as determined by the Fick principle) in ten dogs. The similarity of results with normal circulation and extracorporeal circulation is apparent. At equal flow rates oxygen consumption was approximately 5 per cent higher with normal circulation, a discrepancy which could be due partly to the difference in cardiac work in the two circumstances. The limitations of accuracy in determination of cardiac output by the Fick principle may also account for part of this variation. A linear regression in oxygen consumption is obtained with good correlation within the limits of flow studied in these experiments; however, it is evident that flow and oxygen consumption must meet at zero.



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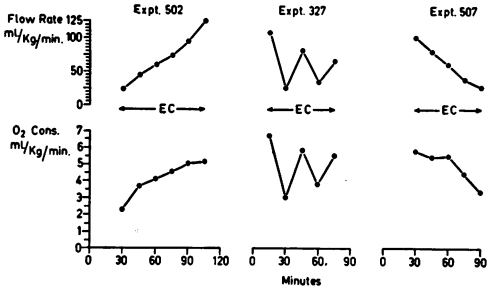

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FIG. 1. Oxygen consumption (as per cent of control level) plotted with EC flow rate. Each point represents a single determination of oxygen consumption at the indicated flow rate. Total determinations: 64 in 16 individual experiments.

For comparison the graph also illustrates oxygen consumption during reduced cardiac output in control experiments (without EC).

The circles each represent a single determination of oxygen consumption at the indicated rate of cardiac output. The dots represent determinations of oxygen consumption at various rates of EC flow.

The small inset shows the calculated regression lines for each set of data, derived as follows:

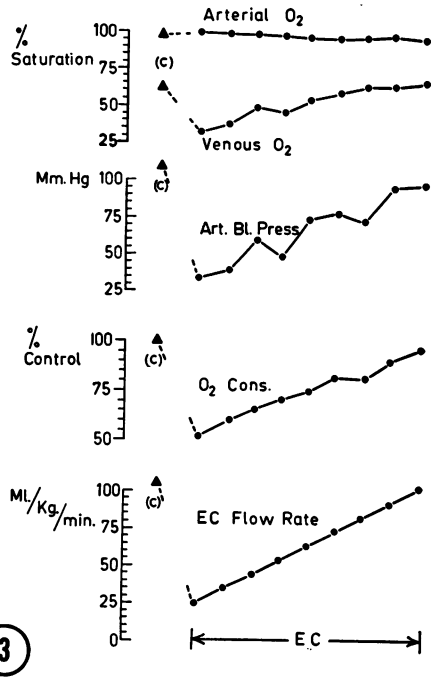
Analysis of O_2 Consumption and EC Flow Rate:

No determinations: 64
$Y = .4437\ (x - 62.7) + 71.6$
Regression Coefficient: .4437
Correlation Coefficient: .83

Analysis of O_2 Consumption and Cardiac Output:

No determinations: 20
$Y = .4515\ (x - 75.75) + 83.3$
Regression Coefficient: .4515
Correlation Coefficient: .92

FIG. 2. Oxygen consumption and EC flow rate plotted in time sequence. Three experiments are illustrated, each with a different order of change in flow rate.



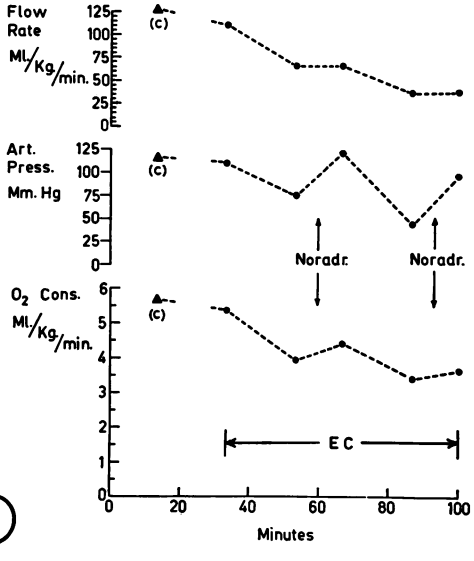


FIG. 3. Mean values from 11 uniform experiments. The initial points in each curve, marked "(c)", represent mean control values. In the curve illustrating flow rate, "control" indicates cardiac output as determined by Fick principle.

FIG. 4. Effect of elevation of blood pressure at low flow rates using noradrenalin. Curves represent mean values of five experiments. The initial points, marked "(c)," indicate control values. In the curve illustrating flow rate, "control" indicates cardiac output as determined by Fick principle.

Because of the possibility that oxygen consumption might be altered at a given level by the effect of the flow rate during the preceding period, the sequence of flow changes was varied in several animals. Figure 2 illustrates three typical experiments, in one of which flow was decreased progressively from high to low, in one flow was alternated between high and low, and in one flow was progressively increased. Oxygen consumption in each instance followed the change in flow rate regardless of the sequence of change.

In Figure 3 are shown average values of oxygen consumption, arterial blood pressure, and arterial and venous oxygen saturations at various EC flow rates in the first 11 experiments; in this group the sequence of change in flow rate, size of animals, and oxygenator capacity was kept uniform. There is a close similarity of the curves of oxygen consumption and increasing flow rate. Although in general arterial pressure rose with increasing flow rate, the change was not linear and the correlation of oxygen consumption to arterial pressure is less close than the correlation with flow rate.* However, in all instances in which mean arterial pressure was over 80 mm. Hg the Oxygen consumption was above 80 per cent of control rate. As flow rate increased the arterio-venous oxygen difference diminished, resulting principally in a progressive rise in venous oxygen saturation.

Effect of Elevating Arterial Pressure with Noradrenalin. Figure 4 illustrates the mean values from experiments in five ani-

* Analysis of Oxygen Consumption and Arterial Pressure:
Number of determinations: 50
$Y = .3687\ (x - 62.6) + 70.9$
Regression Coefficient: .3687
Correlation Coefficient: .67

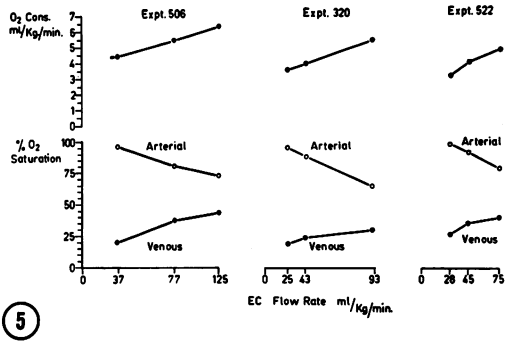
Analysis of Oxygen Consumption and EC Flow Rate:
Number of Determinations: 64
$Y = .4437\ (x - 62.7) + 71.6$
Regression Coefficient: .4437
Correlation Coefficient: .83

mals comparing oxygen consumption (1) at high flow rate, (2) at reduced flow rates, and (3) at reduced flow rates with the arterial blood pressure elevated by noradrenalin. Increasing arterial pressure at low flow rates in this manner increased oxygen consumption slightly, but not to normal levels nor to the level produced by a high flow rate; the increase actually observed with elevation of pressure is not statistically significant ($0.2 > P > .05$). In all experiments a marked increase in the force of cardiac contractions was noted after each administration of noradrenalin, which could account for part of the increase in oxygen utilization which occurred.

Effect of Increasing EC Flow Rate with Simultaneous Decrease in Arterial Oxygen Saturation. Figure 5 shows the oxygen consumption and arterial and venous oxygen saturations at increasing flow rates in experiments with large dogs and restricted oxygenating capacity of the machine. The arterial saturation fell progressively with increasing flow rate, declining to below 75 per cent saturation in each experiment; there was a concomitant rise in venous saturation. Despite the arterial desaturation, increase in flow was accompanied by progressive rise in oxygen utilization.

Comment

The observation that survival was possible with very low circulatory rates [2, 4] undoubtedly was an important stimulus to the development of open heart surgery using extracorporeal circulation. Early experimental studies indicated the possibility of using a portion of a donor's circulation during periods of heart-lung bypass.[9] Subsequently this principle was used in the employment of artificial pump-oxygenators and in experimental and clinical experience with artificial heart-lung machines reported to date low flow rates commonly have been used.



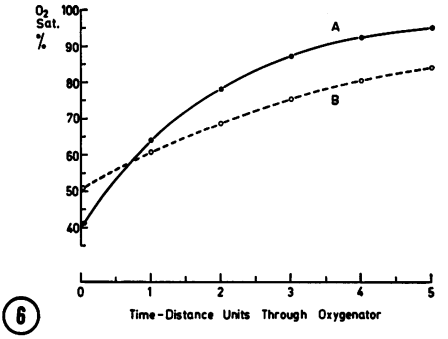


FIG. 5. Three experiments illustrating oxygen consumption at increasing flow rates with a falling arterial oxygen saturation.

FIG. 6. Sample oxygenation curves from an oxygenator of fixed potential operating at maximum efficiency. The abscissa represents a single passage of blood through the oxygenator with the course divided arbitrarily into five equal units which may be considered as either ⅕ the time or ⅕ the distance through the machine. The maximum capability of the oxygenator is employed in curve A to raise the saturation of blood from 40 per cent to 95 per cent at a flow of 500 ml./min., introducing 55 cc. of oxygen per minute into the circulating blood.

At a flow rate of 1,000 ml./min., as illustrated in curve B, saturation increases from 51 per cent to 84.2 per cent (the same mean saturation as at the lower flow rate) and 66 cc. of oxygen are added to the blood per minute.

The present experimental study indicates a considerable decrease in oxygen consumption at low flow rates with implied tissue hypoxia. This would appear to be a limiting factor in the application of the low flow technic for prolonged periods. Certainly the consequences of metabolic acidosis and impairment of organ function, which appear regularly during extracorporeal circulation at low flow rates, add to the in-

herent dangers of an already major operative procedure. Other studies indicate that these aberrations are less severe at high flow rates.[3, 6]

It is not probable that all tissues share equally in the oxygen deficiency at low flows. A redistribution of blood flow may be effected by the body's natural vasoregulatory mechanisms, maintaining a relatively higher circulatory rate in such organs as the heart and brain at the expense of tissues with a greater tolerance to hypoxia. Such a redistribution could be produced by vasoconstriction and reduction in the functioning volume of the vascular bed, and there is evidence that such a mechanism is in effect at low flow rates. When flow rate is increased we have had to add blood to the system; since the amount of blood in the extracorporeal circuit remains constant this would indicate a larger intravascular blood volume at higher flows.

It is important to note that a decline in oxygen consumption does not begin coincidently with a decline from *normal* cardiac output. After completion of the operative manipulations in these dogs, arterial pressure had usually fallen and cardiac output ranged from 15 to 30 per cent below the anticipated basal level in anesthetized dogs, which is usually considered to be 150 to 165 ml./Kg./min.; nevertheless, oxygen consumption remained stable during this period. As cardiac output fell below 100 ml./Kg./min., oxygen consumption began to decline progressively. The same approximate rate also appeared to be the flow required to maintain oxygen consumption at control levels during extracorporeal circulation (Fig. 1).

The importance of circulatory rate as compared to arterial pressure has not been completely defined in respect to their relative effect on oxygen utilization. The evidence obtained here indicates that in terms of total oxygen consumption circulatory rate is the more critical factor; elevation of blood pressure to control levels was not effective in increasing oxygen consumption at low flow rates. The slight increase following administration of noradrenalin may be due in part to the increased cardiac activity caused by this drug. It is possible that distribution of the circulating blood may be modified by noradrenalin but the result of any such shift could not be predicted.

In the presence of a tissue oxygen deficit at low flow rate, the basis for rising oxygen consumption with increasing flow is evident. When the capacity of the oxygenator is high enough to keep the "arterial" blood fully saturated the amount of oxygen offered to the tissues is increased, the venous saturation rises, the capillary-to-tissue oxygen tension gradient is greater, and more oxygen is taken up by the tissues. Conversely, with declining flow rate the venous oxygen saturation falls and the capillary-to-tissue oxygen tension gradient is less favorable.

The rationale is less obvious for an increasing tissue oxygen consumption at higher flow rates when the arterial saturation is declining due to limited capacity of the oxygenator. However, even in this event a greater amount of oxygen is offered to the tissues. In an oxygenator of fixed capacity, at higher flow rates the saturation of the blood increases in a more linear fashion as it passes through the oxygenator; therefore the actual effectiveness of oxygenation is increased and more oxygen can be added in a single passage. Figure 6 illustrates this relation in a given oxygenator at two rates of flow; it is seen that at the higher rate of flow, with a larger amount of oxygen added to the blood in a single passage, the arterial saturation has declined but the venous saturation has increased and the mean saturation is the same as at the lower flow rate. This qualitative relationship will remain valid at any change in flow. If oxygen demand (and consumption) should be further increased at higher flow rates, the desaturation would be exaggerated as occurred in these experiments. This augmen-

tation of *effective* demand may be partly a result of the expanded vascular bed and an increased proportion of functioning capillaries at higher flow rates. Since the relative distribution of this increased flow could not be measured, the net benefit to any given organ is indeterminate: however, the increased consumption obviously represents an alleviation of the total deficit existing at lower flow rates.

Application to human patients of the data obtained in these experiments presents certain problems beyond those frequently encountered in relating animal studies to humans. The cardiac output, circulating blood volume, and metabolic rate are higher per unit weight in dogs than in humans. However, it is probable that the qualitative relationships illustrated in these experiments would be valid in humans and a similar relation between oxygen consumption and flow rate has been noted in patients operated upon at this institution.[7]

Summary

Experiments were carried out in dogs to study oxygen consumption during extracorporeal circulation with an artificial heart-lung machine and to evaluate factors affecting oxygen utilization. The following observations were made:

1. At low flow rates (20–30 ml./Kg./min.) oxygen consumption was reduced to approximately 50 per cent of control levels. With increasing flow oxygen consumption rose, reaching control levels at flow rates of approximately 100 ml./Kg./min.

2. The relation of oxygen consumption during EC to decreasing flow rate is similar to the relation of oxygen consumption to reduced cardiac output.

3. The relation of oxygen consumption to flow rate is not appreciably altered by the sequence of change in flow rate.

4. The decline in oxygen consumption at low rates of flow appeared primarily due to the decreased circulatory rate rather than to the concomitant fall in arterial blood pressure. Elevation of blood pressure with noradrenalin produced a slight increase in oxygen utilization at low flows, but not to control levels nor to the extent produced by elevating the flow-rate.

5. With oxygenators of limited capacity, or subjects too large for the capacity of the oxygenator, arterial saturation fell progressively with increasing flow rates; nevertheless the higher flow rates consistently allowed a greater oxygen utilization.

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