Effect of Hypoxia on Myocardium in Heart-Lung Preparation. (32565)

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The circulatory responses to acute hypoxia have been under investigation for many years (1,2,3). It has been reported that mild hypoxia(10-12%) induces an increase in heart rate, cardiac output, and blood pressure (4,5,6). The heart rate and cardiac output are likely to fall either if exposure to such levels of hypoxia is prolonged or if severe levels of hypoxia are induced(7,6). It has generally been believed that the terminal cardiovascular failure is due to weakness of oxygen starved heart muscle(8,6). On the other hand, some experiments indicate that hypoxia may increase the contractile strength of the heart through a direct influence on the myocardium(9,10).

Because cardiovascular response to hypoxia results from a complex interaction of direct effects on the heart or indirect effects *via* nervous or humoral control, or both, the question of direct action of hypoxia *per se* on myocardium is not fully explained or agreed upon. In our experiments an isolated heart-lung preparation (HLP) was selected in preference to the intact animal so that the direct action of hypoxia on the heart could be investigated specifically. The oxygen tension of blood was changed by ventilating the lungs with gas mixtures containing various amounts of oxygen. In a few pilot experiments, an attempt was made to study the metabolism of carbohydrate by heart muscle at various arterial oxygen tensions.

Methods. Heart-lung preparations according to the method of Starling(11) were prepared from mongrel dogs weighing 7.7 to 10 kg. They were ventilated with a pump connected to a spirometer filled with gas mixtures varying in content from 2.5 to 45% O_2, 4% CO_2 with the balance N_2. The preparations were supported by a continuous infusion of glucose (10 mg/min) and insulin (0.008 unit/min)(12). Respiratory CO_2 and O_2 were measured continuously with a Beckman Model LB-1 gas analyzer and a Model E2 Oxygen Analyzer, respectively.

The following parameters were recorded: (a) pressures from the left subclavian artery and the left atrium with Statham pressure transducers; (b) the systemic flow with a Wilson flowmeter; (c) the pulmonary flow with a pulsed field electromagnetic flowmeter. A portion of the systemic flow was shunted through a modular cuvette for continuous measurements of pO_2, pCO_2, and pH of the blood. The details of the experimental design, instrumentation, and calibrations are explained elsewhere(13).

In all experiments arterial pCO_2 was maintained at 30 mm Hg to 36 mm Hg and arterial pH ranged from 7.35 to 7.40. No significant changes were noted in arterial pCO_2 and pH at various levels of hypoxia.

When the gaseous oxygen mixture was altered, 8 to 10 minutes were allowed until a new steady level was reached. This level was then sustained for an additional 25 to 30 minutes.

For chemical analyses 4 ml samples of arterial blood were collected in weighed cold centrifuge tubes containing 6 ml of 10% trichloracetic acid. Each tube was reweighed and centrifuged immediately. The blood glucose was determined by the anthrone method (14); lactate and pyruvate were measured enzymatically(15,16). The performance of the heart was evaluated by a comparison of curves relating left atrial pressure (LAP) to left ventricular stroke work (SW). SW was computed from pulmonary or systemic flow $\times$ the mean aortic pressure/heart rate. Ejection (ml) $\times$ arterial pressure (mm Hg) was converted to g cm approximating the density of dog blood as 1.045. The work load was varied by changing the flow and keeping the arterial pressure constant. Since the heart rate changes were small and all data were considered on the basis of the relationship of

atrial pressure to stroke work, effects of heart rate are not considered here.

Results. In the early part of this study a comparison was made of the stroke work of the left ventricle when various amounts of respiratory oxygen were present. Data from the 18 preparations in which respiratory gas compositions were recorded without blood gas studies were in essential agreement with the later experiments in which blood gas measurements were also made. In general, the performance of the heart was not depressed and in some cases was even improved as the respiratory oxygen content was reduced from 21 to 4%. At 3% oxygen the heart showed a clear sign of depression in its performance as judged by an increase in left atrial pressure at any given stroke work.

Fig. 1 shows that in a total of 40 dog hearts tested, there was no definite change in heart rate with change of arterial pO_2. In each experiment the HLP was subjected to two or three levels of hypoxia.

Fig. 2 presents data from a single preparation typical of 14 experiments in which work curves were made at arterial oxygen tensions of 250, 115, 37, 24, and 17.5-18.5 mm Hg. The work curves in the upper graph

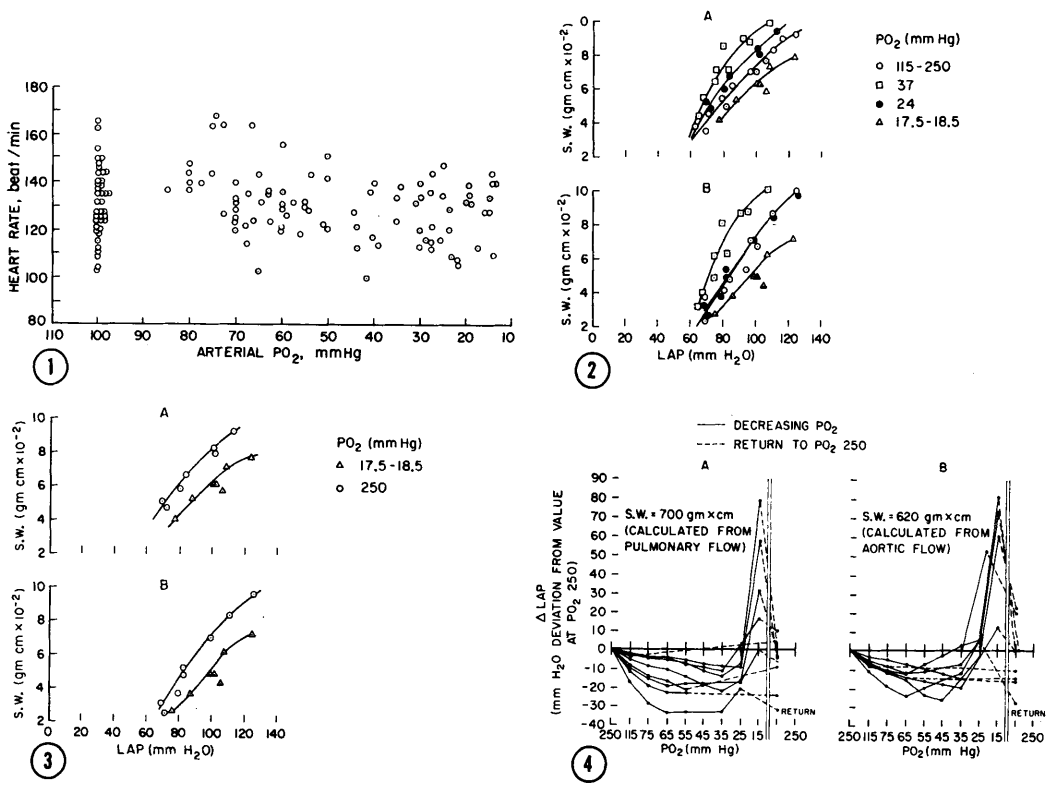

FIG. 1. Relationship between heart rate and arterial pO_2 in 40 heart-lung preparations (HLP). In each HLP the heart rate was recorded at pO_2 of about 100 mm Hg and 2 or 3 lower pO_2 levels. Data are combined because no significant change in the heart rate was noted at lower pO_2.

FIG. 2. Effect of low arterial pO_2 on left ventricular performance. The performance was evaluated by the relationship between left atrial pressure (LAP) and stroke work (SW). SW was changed by varying flow-aortic pressure constant. (a) SW calculated from pulmonary flow. (b) SW calculated from aortic (systemic) flow.

FIG. 3. Left ventricular performance with increasing pO_2, showing recovery from effect of hypoxia. (a) SW calculated from pulmonary flow. (b) SW calculated from aortic flow.

FIG. 4. Left ventricular performance at varying pO_2. In all these experiments SW was kept constant. ΔLAP represents the change from the value at pO_2 = 250 mm Hg. Step-wise change of pO_2 shown on the abscissa. Each line represents a single experiment. The dotted lines represent change of LAP after pO_2 was returned to 250 mm Hg.

are computed on the basis of pulmonary flow and mean aortic pressure, those in the lower graph on the basis of systemic flow and mean aortic pressure. The upper graph shows that the performance improves both at 37 and 24 mm Hg oxygen tension, but is impaired at pO_2 of 18 mm Hg. The improvement is greater at pO_2 of 37 than 24 mm Hg. The lower graph indicates improvement at pO_2 of 37 mm Hg, no change at pO_2 of 24 mm Hg, and a greater impairment in the "systemic work" at pO_2 of 18 mm Hg than in the "pulmonary work." This quantitative difference between the two graphs is due to change in coronary circulation at low pO_2. The pulmonary computation represents the total work of the left ventricle and reflects the energy transformation by the myocardium. The systemic computation, on the other hand, excludes the coronary circulation (which was increased by hypoxia as judged by the difference of pulmonary and systemic flow) and serves to indicate changes in the total circulatory effectiveness of the heart.

Fig. 3 demonstrates that the performance is restored to normal at higher pO_2. This recovery begins immediately when the arterial oxygen tension is increased.

Fig. 4 presents the results of lowering pO_2 from 250 mm Hg by steps to 15 mm Hg and finally returning to 250 mm Hg. The ordinate shows the resulting change of LAP from the initial values. Stroke work was maintained constant at 700 g cm. When we consider the work curves based on the computation of the pulmonary flow (the left hand graph), it is clear that in 8 out of 9 cases, lowering the pO_2 to 33 mm Hg induces an apparent improvement in the performance of the heart. In other words, in all cases, the heart is doing the same work at lower filling pressures at pO_2 35 as at 250 mm Hg. For the reasons just mentioned, the improvement in circulatory effectiveness (systemic) is less evident.

In 5 heart-lung preparations, heart performance was correlated with metabolic changes at low oxygen tension (Fig. 5). The performance was measured at pO_2 of 250 or 100 mm Hg; 33-38 mm Hg; 17-22 mm Hg; return to 100 or 250 mm Hg, for 30 minutes at each level of oxygen tension. At the beginning and end of each period, duplicate arterial

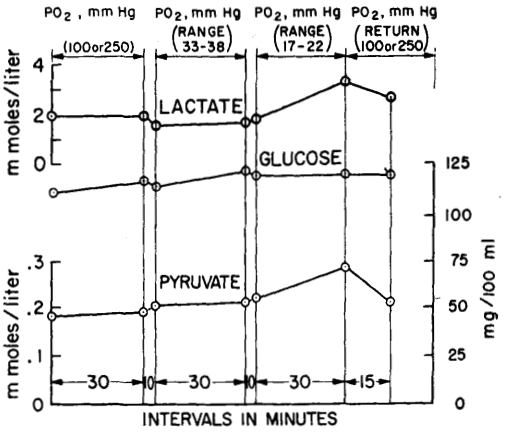

FIG. 5. Changes in blood lactate, glucose, and pyruvate concentration in the hypoxic heart-lung preparation. See text.

blood samples were taken for determining glucose, lactate, and pyruvate. There was no difference in values at pO_2 of 100 mm Hg and 250 mm Hg; therefore, these values were combined. Fig. 5 shows that there is no clear change in lactate and pyruvate levels of the blood at pO_2 of 250 and 33 mm Hg. However, at oxygen tension of 22 mm Hg or less, the lactate level of the blood increases 65% and the pyruvate level 40%. This indicates an increase in anaerobic metabolism and suggests that oxygen delivery has become a limiting factor in the rate of energy utilization. With restoration of oxygen tension, both lactate and pyruvate levels were lowered.

Discussion. The performance of the hearts subjected to a change in arterial oxygen tension in the range of 250 to 15 mm Hg was evaluated by comparing the left atrial pressures at constant stroke work. In general, our results indicate that the performance of a heart improves with mild hypoxia (pO_2 70-35 mm Hg) and begins to decline under severe hypoxia. The depressed heart can be quickly restored by an increase in the blood oxygen tension.

The cause of the improved performance of the heart under mild hypoxia has not been resolved in this study. The limited chemical studies made were designed rather to throw light on the deterioration with severe hypoxia. It is possible that mild hypoxia may effect an intramyocardial liberation of catecholamines and/or a histamine-like agent(17,9,18). We

might expect the heart to perform more effectively in the presence of inotropic catecholamines as long as the availability of oxygen does not fall below a critical level, but after that the performance would begin to decline. In some of our experiments the heart performed better at normal oxygen tension after severe hypoxia than it did before. This may have resulted from release of catecholamines during mild or severe hypoxia, the released catecholamines manifesting their maximum activity when adequate oxygen tension was restored. (See the dotted lines in Fig. 4.)

Our results are in accord with Penna and his co-workers, who showed that hypoxia induces an increase in myocardial contractile force in an isolated guinea pig atrium bathed in Tyrode solution(9). Kahler and Braunwald's (19) studies, on the other hand, indicate that the contractile strength is decreased when the heart is perfused with hypoxic blood.

The study of carbohydrate metabolism in some of the experiments showed no changes in blood lactate and pyruvate levels until the arterial oxygen tension was at or below 22 mm Hg at which level their concentrations rose markedly. The accumulation of these metabolites was reversed with a return to normal or above normal oxygen tension. We believe that the accumulation of lactate and pyruvate under our controlled experimental conditions (constant rate of ventilation, pH, CO_2 tension, and blood glucose level) is clear evidence of an increase in anaerobic metabolism. This belief is further supported by a decline in their levels on return to normal oxygen even though the continuous infusion of glucose kept the blood glucose at the normal level. Therefore, heart performance is depressed when the aerobic metabolism is markedly reduced as a result of lack of oxygen.

Finally, we conclude that diminishing oxygen tension produces a biphasic cardiac response, being positively inotropic from pO_2 of 100-35 mm Hg and negatively inotropic at lower values. The negative inotropic effect is accompanied by demonstrable metabolic changes. The negative inotropic effect and the metabolic changes are both reversible.

Summary. Starling heart-lung preparations were ventilated with various mixtures of oxygen, nitrogen, and carbon dioxide and the performance of the heart was evaluated by relating stroke work to left atrial pressure. At oxygen tensions of arterial blood between 65 mm Hg and 25 mm Hg performance improved. At 20 mm Hg or lower the performance was impaired but the impairment was reversible. The impairment was accompanied by an accumulation of lactate and pyruvate in the blood which also was reversible as oxygen tension was restored. Possible mechanism of these changes is discussed.

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