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Mechanical Response of the Isolated Mammalian Heart to Anoxia.*

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The circulatory response to anoxia, in the intact animal, has been studied in a variety of ways and under a variety of circumstances.[1-7] All investigators are agreed that an increase in cardiac output occurs with moderate degrees of arterial desaturation. This response has been attributed[7] to a stimulating effect of anoxia directly upon the myocardium, though in no one set of experiments is it clear that all extra-cardiac factors have been rigorously excluded. Furthermore, experiments with the heart-lung and isolated heart preparations[8,9] under anoxia have not supported this view.

The present studies on the isolated heart were undertaken as part of a broader program to evaluate the factors in tolerance to altitude. When it became apparent that the myocardium, at least as examined in these experiments, was not a limiting factor, the studies, of necessity, were discontinued. However, a considerable body of data was accumulated bearing on the question alluded to at the outset, and it is essentially for this reason that a brief report of the work is here presented.

Method. Cats were used in all experi-

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1 Harrison, T. R., Wilson, C. P., and Blalock, A., *J. Clin. Invest.*, 1925, **1**, 547.

2 Sands, J., and DeGraff, A., *Am. J. Physiol.*, 1925, **74**, 416.

3 Harrison, T. R., and Blalock, A., *Am. J. Physiol.*, 1927, **80**, 169.

4 Harrison, T. R., Blalock, A., Pilcher, C., and Wilson, C. P., *Am. J. Physiol.*, 1927, **83**, 284.

5 Gollwitzer-Meier, K., *Pfluger's Arch.*, 1928, **220**, 434.

6 Strughold, H., *Am. J. Physiol.*, 1930, **94**, 641.

7 Wiggers, C. J., *Ann. Int. Med.*, 1941, **14**, 1237.

8 Gremels, H., and Starling, E. H., *J. Physiol.*, 1926, **61**, 297.

9 Bogue, J. Y., Chang, I., and Gregory, R. A., *Quart. J. Exp. Physiol.*, 1937-38, **27**, 319.

ments, the heart being completely isolated according to a technic previously described,[10] except that the ventilating gas, or gas mixture, was passed directly from a tank through a moisture bottle and into the oxygenator, from which it escaped freely.

After cardiac output and cardiac volume had become stable, nitrogen was substituted for the oxygen used initially. In 7 of the 17 experiments in which complete flow readings were made, 5% CO_2 was used in both the oxygen and nitrogen. The resultant anoxia was progressive in character and provided a period of about 10 to 30 minutes, depending upon the preparation, during which the behavior of the heart over a wide range of oxygen tensions could be observed. After a measured and uniform increment in cardiac volume had occurred, oxygen, or oxygen + 5% CO_2 was readmitted.

The hearts in every case were fresh and in good condition. Except for minor fluctuations, filling and emptying pressures were maintained constant throughout.

[10] Lorber, V., *Am. Heart J.*, 1942, **23**, 37.

In 8 additional experiments, 5 with and 3 without CO_2, measurements of the pH of arterial and venous bloods were made with the glass electrode at various stages of the procedure. Blood lactate values were followed in 3, and blood glucose and lactate values, in 4 other experiments. In 8 separate experiments, measurements of the oxygen content of the arterial blood were made with the manometric Van Slyke apparatus at various times. In all, over 40 experiments were carried out in 19 preparations.

Results. Cardiac volume. Behavior prior to the onset of dilatation varied with the presence or absence of CO_2 in the ventilating gas mixture. In the experiments without CO_2, with few exceptions, there was a slight to marked decrease in heart volume immediately following the onset of anoxia. When CO_2 was present, cardiac volume remained unchanged or increased slightly early in anoxia. Following this period, dilatation commenced, and, once established, progressed rapidly. At an arbitrarily selected volume increment, oxygen was readmitted. In those experiments carried out with CO_2 in the ven-

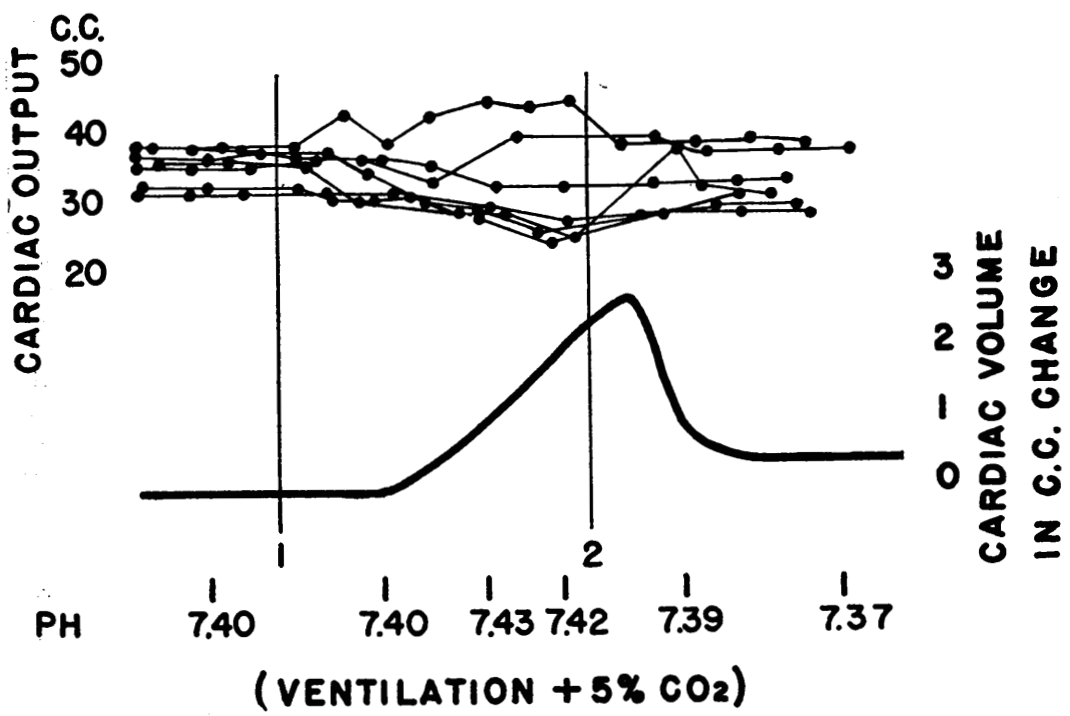

FIG. 1.

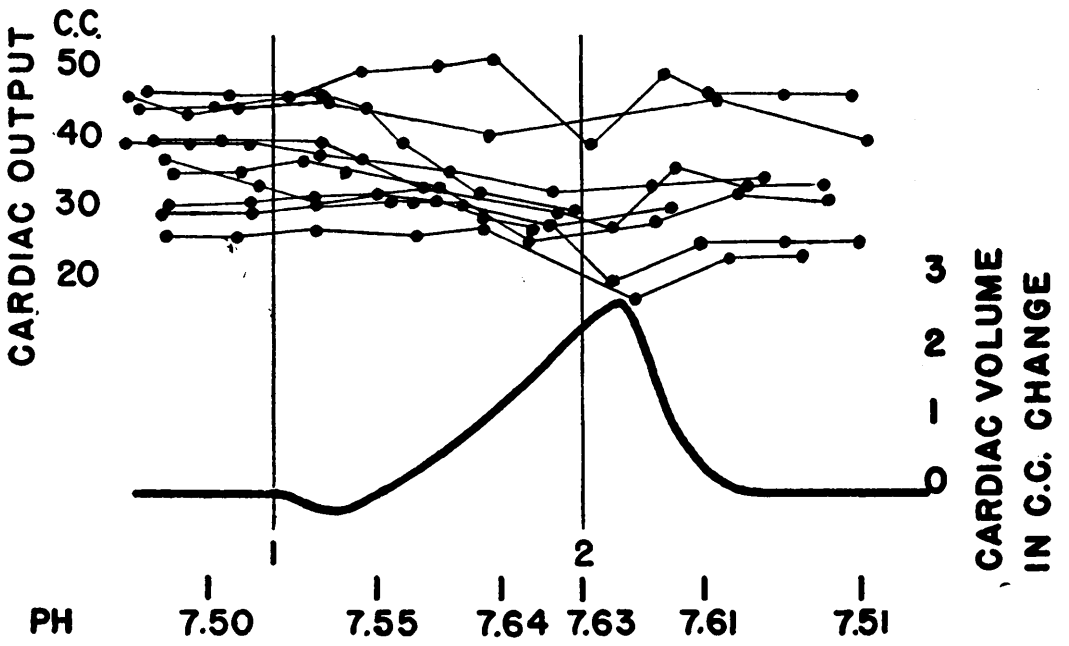

FIG. 2.

tilating mixture, recovery to the initial volume was not complete in most instances.

The time from the onset of anoxia to the readmission of oxygen varied widely from preparation to preparation (9 to 34 min.), but in any one preparation, the first two trials usually checked to within 1-2 minutes. With repeated trials, dilatation occurred more quickly. An effort was made to relate the dilatation times in some probable way to every physical and chemical factor of which measurements were made (including heart weight, coronary flow, external work, and blood volume, in addition to those already listed), but without success. The fact, however, that this response is a characteristic of the preparation, for whatever reason, permits each preparation to serve as its own control in experiments designed to test the influence of various agents on the response to anoxia.

The first detectable response to desaturation was an increase in the coronary flow. Dilatation did not begin, however, until oxygen tensions were very low. In 7 experiments in which measurements of the oxygen content of the arterial blood were made at the onset of dilatation, this occurred at about 50% (44 to 65) saturation, or at oxygen tensions of 10-15 mm Hg., under the conditions of the experiment (CO_2 absent from the ventilating gas). Subsequent experiments employing more gradual desaturation have been carried to even lower oxygen tensions before the appearance of dilatation. Though no measurements of oxygen were made, it was quite apparent that dilatation occurred much more readily in experiments in which CO_2 was present in the ventilating gas.

In the pH measurements a plausible explanation was found for the peculiar drop in cardiac volume seen early in preparations ventilated without CO_2. In these, increases of pH of as much as 0.2 unit were recorded in the course of desaturation, and appreciable differences were already in evidence when the volume dip appeared. In experiments with CO_2, on the other hand, elevations appeared later and only reached about one-third the magnitude noted above.

In Fig. 1 and 2, composite graphs of the results of experiments with and without CO_2, respectively, are presented. The heavy, peaked curves represent cardiac volume. The interval between ordinates 1 and 2 represents the period of anoxia. The pH values are from two experiments made on the same

preparation, ventilating with and without CO_2. Measurements were made on the coronary blood and are entered on the abscissa at points appropriate with respect to the cardiac volume.

Cardiac Output. Of the 10 experiments without CO_2 in the ventilating gas, 5 showed an early increase in output of between 5 and 10%, one, a decrease of 10%, and 4, no significant change. Output tended to decline moderately with progressing desaturation, and on readmission of oxygen, was restored to pre-anoxic levels in most cases. Increases in output were accompanied by increased coronary flow, and decrements in emptying pressure of from 3 to 6 mm Hg due to the lowered peripheral resistance resulting from coronary dilatation. This factor alone, in the presence of constant filling pressure, could readily account for the increased output. However, it is apparent that if cardiac volume had been maintained constant in the early period, rather than permitting the usual fall, a further increase in output would have been recorded. In a subsequent experiment employing more gradual desaturation, a 32% increase in output was recorded early in the experiment, at constant cardiac volume and emptying pressure.

In the 7 experiments in which CO_2 was present in the ventilating gas, cardiac output was increased significantly (15%) early in anoxia in but one case, at which time the increment in coronary flow and decrement in emptying pressure were already quite appreciable. One late increase, when these factors were quite marked, was noted. Otherwise, the general course of the cardiac output was as described for the first group of experiments.

The results on output for all experiments are presented in Fig. 1 and 2. The interval between the ordinates 1 and 2 represents different time intervals in different experiments.

Discussion. When the completely isolated mammalian heart is subjected to anoxia, increased output that cannot be accounted for on a hemodynamic basis results only when CO_2 is absent from the ventilating gas, and is in all likelihood a function of the altered pH met with under these circumstances. As such, it must be regarded as a systematic artefact, rather than a physiological response of the cardiac muscle to anoxia. When 5% CO_2 is present in the ventilating gas, an increased output of purely cardiac origin is lacking. The elevations in the blood pH under these circumstances are similar in magnitude to those measured in the intact animal in anoxia.[3]

The caution with which results from experiments of this type must be considered in relation to problems involving the intact animal is emphasized by the recent experiments of Keys, Stapp, ond Violante.[11] These observers found altitude tolerance in normal young men increased by the presence of CO_2 in the inspired air. The isolated heart is affected adversely. However, the impression gained from the present experiments that cardiac muscle is hardly the limiting factor in tolerance to hypoxia, is well substantiated by Keys *et al.*, who found no evidence favoring a drop in cardiac efficiency at oxygen tensions at which syncope occurred.

Conclusions. 1. The depressant effects of anoxia on the completely isolated mammalian heart appeared at oxygen tensions well below those tolerated by the intact animal. The heart muscle, therefore, at least as examined in the present experiments, cannot be regarded as a limiting factor in tolerance of the intact animal for anoxia. 2. Increases in cardiac output (of purely cardiac origin) by the isolated heart under anoxia are seen only when CO_2 is absent from the ventilating gas. The effect appears to be due to the marked elevations in pH seen under these conditions, and, as such, is regarded as a systematic artefact rather than evidence of a direct stimulating effect of low oxygen tensions on the myocardium.

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[11] Keys, A., Stapp, J. P., and Violante, A., *Am. J. Physiol.*, 1943, **138**, 763.