Contractility, Metabolism and Pharmacological Reactions of Isolated Gas-Perfused Cat Hearts

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ABSTRACT

Cat hearts were perfused through the aorta with substrate-free Krebs solution for 5 min, then with 5% CO₂-95% O₂ saturated with water vapor at 37.5°C. Heart rate decreased rapidly but contractility was maintained at pre-gas levels for 3 to 4 hours, decreasing to 25% at 10 hours. Driving the preparations at 168 beats/min did not appreciably change the time course of change in contractility. The hearts developed more tension at all resting tensions and were able to perform more work than hearts perfused with substrate-free Krebs solution, but their work capacity was less than that of hearts perfused with glucose-Krebs solution. They reacted normally to sympathomimetic amines and blocking agents. They were very sensitive to increases in perfusion pressure, developing completely reversible arrhythmias at pressures 80 to 150 mm Hg above the control (60 mm Hg). Most hearts developed contractile alternans which usually was not accompanied by electrical alternation. Glycogen, lactate, pyruvate content decreased rapidly, the first to a residual level and the others to undetectable levels.

ADDITIONAL KEY WORDS

glycogen loss heart rate prolonged survival
mechanical alternation Starling relationship pressure arrhythmias

As early as 1902, Magnus (1) maintained a beating cat heart for 1 hour while perfusing it with gaseous oxygen. Burns et al. (2) repeated this experiment and described the relationship between the perfusing pressure and the flow of gas through the coronary arteries. Sabiston et al. (3) and Talbert et al. (4) described a technique for gas perfusion with which electrical, but not mechanical, activity could be maintained for periods approaching 8 hours.

The liquid media used to perfuse the isolated heart perform several functions: (A) maintenance of a constant temperature and ionic environment, (B) supply of oxygen, (C) supply of energy-yielding substrates, and (D) removal of metabolic end products. Perfusion with a gaseous medium may maintain a constant temperature and a supply of oxygen, but is obviously incapable of supplying or removing metabolites other than CO₂.

It is well documented (5-7) that the isolated heart fails rapidly when perfused with a substrate-free liquid medium. This paper describes a procedure for gas perfusion of the isolated cat heart which allows contractility to remain stable for periods exceeding 3 hours, and it compares gase- and liquid-perfused hearts with respect to contractility, performance of work and response to pharmacological agents.

Methods

PERFUSION SYSTEM

We were unable to maintain contractility using the procedures of Burns et al. (2) or of Sabiston et al. (3) primarily because of difficulties in regulating the temperature of the gaseous perfusate. An apparatus was constructed which permitted both close temperature control of the...
humidified gas mixture at various flow rates and rapid switching from liquid to gas perfusion (Fig. 1). The heart was perfused by the Langendorff technique from a cannula with four side arms close to its tip. Two thermistor probes (YSI Models 402 and 403) extended directly into the perfusate flowing through side arm A. One was used to monitor temperature, the other functioned in conjunction with a temperature regulator (YSI Model 63) which controlled the flow of current through a heating coil placed around the glass tube leading to the cannula. This coil served only as a final temperature adjustment (see below) and maintained the temperature of both liquid and gaseous perfusates at 37.5 ± 0.4°C. During gas perfusion, side arm B was connected by a stopcock (S-3) and a trap to a gas pressure regulator (PR) constructed by immersing a glass tube into a column of water to a depth corresponding to 60 mm Hg. The trap collected liquid perfusate contained in the system at the time of change from liquid to gas perfusion. Side arm C was connected to a Statham P 23D pressure transducer (PT). A thin plastic tube used for injection of drugs passed through side arm D and terminated in the cannula close to its point of insertion into the aorta.

Liquid perfusates of different composition were stored in reservoirs placed level with the heart, pressurized to 60 mm Hg with 95% O₂ and 5% CO₂. The liquid passed through a water-jacketed spiral condenser which served as a heat exchanger, and then through stopcocks S-1 and S-2 before reaching the cannula. Stopcock S-1 selected either reservoir; stopcock S-2 selected either gas or liquid perfusate.

The 95% O₂ and 5% CO₂ mixture for perfusion was preheated in a water-jacketed condenser and was then humidified in a water-jacketed gas scrubbing bottle containing distilled water. It then passed through glass wool which removed water droplets and was led to stopcock S-2.

The heart was enclosed in a water-jacketed Lucite box. High humidity was maintained in the chamber by a fan which circulated air past several vertical strips of moist filter paper. A funnel under the heart passed through the bottom of the box for recovery of liquid perfusate. The water circulating through all jacketed components was supplied from a constant-temperature bath at 40.0 ± 0.5°C.

In those experiments in which liquid perfusate was used exclusively, the perfusion system was changed to allow recirculation of the perfusate. Our apparatus was similar to that of Bleehen and Fisher (8) except that the perfusate was recirculated by a pump instead of an air lift and the pressure was supplied by the equilibrating gas instead of gravity. The total volume of liquid in our system was 200 to 250 ml.
THE GAS-PERFUSED CAT HEART

PREPARATION OF THE HEART

Kittens of either sex weighing 0.4 to 1.2 kg were fed a diet of meat, fish and eggs ad libitum for at least 2 days before use. The animals were killed by a blow on the head and the hearts removed and placed in a beaker of cold Krebs-Henseleit-bicarbonate solution. Anticoagulants were not used because of their possible effects on tissue metabolism (9).

The hearts were cleaned of extraneous tissue and a small slit was made in the walls of each ventricle. The aorta was then cannulated and the heart connected to the perfusion apparatus. A 5-min period of liquid perfusion preceded gas perfusion in all experiments. Ten seconds of gas perfusion was used to clear the vasculature before weighing hearts which had last been perfused with liquid. The liquid perfusate was substrate-free Krebs-Henseleit solution gassed with 95% O2 and 5% CO2; it contained NaCl, 118.0 mM; KCl, 4.7 mM; KH2PO4, 1.2 mM; CaCl2 * 2H2O, 2.5 mM; MgSO4, 2.4 mM and NaHCO3, 28.0 mM. Glucose (2.0 g/liter) was added only for the experiments in which work capacity was determined.

MEASUREMENTS

Isometric contractility was measured with a Grass FT-03 force-displacement transducer attached to a string sewn to the ventricular apex; resting tension was defined as the diastolic tension exerted on the apex. Isotonic contractility and external work were measured electronically with an apparatus in which work was estimated from the lifting of imposed weights attached to the apex of the ventricle (10).

Heart rates were determined from the recordings of contractile force. Some hearts were driven electrically through small clip electrodes placed on the right atrial appendage and ventricular apex. Suprathreshold rectangular pulses (4 to 8 v) of 5 msec duration were supplied by a Grass SD-5 stimulator. Electrograms were obtained using electrodes placed in the same positions as the stimulating electrodes. Recordings were made with a Grass polygraph.

Analytical Methods

Only the ventricles, cut below the fat pad surrounding the circumflex artery, were used for analysis. They were blotted with tissue paper and then dropped into liquid nitrogen. The frozen tissue was placed in steel test tubes previously cooled with liquid nitrogen and powdered by percussion. The powder was mixed by stirring and stored at -20°C. Aliquots of tissue powder were weighed rapidly and analyzed as follows:

Water content. This was calculated from the weight loss after drying to constant weight at 80°C in vacuo. This value was used to calculate the dry weight of aliquots used for other analyses.

Glycogen and total carbohydrate. Samples were hydrolyzed in 50% NaOH and glycogen precipitated with cold 80% methanol. Other samples were homogenized in 5% trichloroacetic acid to extract total tissue carbohydrate. The glycogen precipitate and the trichloroacetic acid extract were analyzed spectrophotometrically by the sulfuric acid method of Kemp and Kits Von Hejningen (11). Results are expressed as glucose equivalents.

Lactate and pyruvate. Cold 6% perchloric acid extracts were analyzed by enzymatic methods (12, 13). The reagents were obtained from Sigma Chemical Co., St. Louis, Mo.

Results are expressed as micromoles per gram dry weight. Data for each group of hearts are expressed as means ± their standard errors. The significance of differences between groups was estimated by Student's t test.

DRUGS USED

Stock solutions of epinephrine bitartrate, nor-epinephrine bitartrate, isoproterenol hydrochloride, pronethalol hydrochloride and cocaine hydrochloride containing 10 mg/ml of the bases were made in acidified 0.9% NaCl, and further dilutions made with the same vehicle on the day of each experiment; 0.05 to 0.1 ml of the appropriate dilution was made to 1 ml with Krebs-Henseleit solution immediately before administration. In later experiments it was found that more reproducible results were obtained if the drugs were injected in a volume of 5 ml.

RESULTS

CONTRACTILITY AND HEART RATE

Isometric contractile force and heart rate at a constant resting tension of 10 g were measured in two groups of hearts. The first was perfused for 2 hours with recirculating substrate-free Krebs-Henseleit solution (6 hearts). The second group (4 hearts) was perfused with gas for 10 hours after 5 min of perfusion with liquid. Contractile force and rate at the end of 5 min of liquid perfusion were taken as the initial (control) values in both groups.

Figures 2A and 2B show that the changes in contractility and rate resulting from long periods of perfusion were strikingly different under the two conditions. Figure 2A shows that the rate of liquid-perfused hearts declined throughout the 2-hour period of the experiments, reaching 73 ± 6% of the initial
value of 163 ± 8 beats/min at the end of the experiments. The rates of gas-perfused hearts fell rapidly during the first hour to a value of 43 ± 3% of initial but declined only slowly during the remaining 9 hours. The contractile force of liquid-perfused hearts declined continuously throughout the experiment (Fig. 2B). It was 50% of the initial value after 80 min and 10% of initial after 120 min. The contractility of gas-perfused hearts increased significantly during the first 20 min and remained above the initial level for 100 min. No statistically significant fall below the initial level was observed before the fourth hour of gas perfusion. The contractile force continued to decline slowly, reaching a value of 50% of initial at 7 hours and of 25% of initial after 10 hours, at which time the experiments were terminated. A third group (4 hearts) was perfused with gas for 7 hours while being driven at a rate (168 beats/min) close to the initial rate of liquid-perfused hearts. The contractility of these hearts was only slightly less than that of the other gas-perfused group. The increase in contractile force above the initial value, of 75 min duration, was not statistically sig-
nificant; 50% of control was reached after 5 hours and 25% of control after 7 hours.

In agreement with the observations of Cattell and Gold (14) and Luisada and Weiss (15), we observed that hearts maintained on liquid tended to shorten gradually throughout the period of perfusion and it was necessary to adjust the force-displacement transducer in order to maintain the 10 g resting tension. This did not occur in gas-perfused hearts. When gas perfusion was started after 2 hours of liquid perfusion, diastolic tension decreased to the control within 3 min but contractile force increased only 20%.

Contractions of alternate strength (contractile alternans) were observed in 90% of more than 50 hearts perfused with gas. This usually began during the first 15 min. The difference between alternate contractions, very small initially, increased during the next 45 min and then remained constant for the remainder of the experiment. Contractility during alternans is expressed as the arithmetic mean of the alternating beats. The curve relating contractility to time for any 1 heart shows a slight dip of less than 5 min duration immediately after onset of contractile alternans, followed by a continuing increase in average contractility. This is not seen in the composite curve (Fig. 2B) because of variations in the time at which alternation began.

Electrograms were obtained from 37 hearts with contractile alternans. No electrical alternans was seen in 27 of these (73%). The weaker beat in each of these hearts began only after relaxation from the stronger beat was complete (Fig. 3B). The weaker beat in each of the 10 hearts which did show electrical alternans began before relaxation was complete (Fig. 3A).

Many experimentally induced arrhythmias are affected by changes in perfusion pressure (16, 17). We observed that increasing the perfusion pressure from 60 to more than 100 mm Hg caused multifocal ventricular arrhythmias which continued until the pressure was lowered (Fig. 4). In 6 gas-perfused hearts the mean pressure threshold for the initiation of the arrhythmia was 124 ± 9 mm Hg, whereas it was 187 ± 12 mm Hg in 6 liquid-perfused hearts. The contractility and electrical activity of the latter group did not return to control conditions when the pressure was lowered. Gas-perfused hearts did not show these irreversible changes. The pressure threshold for arrhythmia production could

![Figure 3](http://circres.ahajournals.org/)

**Figure 3**

Contractile alternans during gas perfusion. The upper tracing is an electrogram; lower tracing shows isometric contractile force. In A, electrical alternans accompanies mechanical alternans. In B, recording from another heart shows mechanical alternans only.
Response of a gas-perfused heart to increased perfusion pressure. Electrogram recorded with electrodes on right atrial appendage and on ventricular apex. The arrows indicate threshold pressure (120 mm Hg) for induction of arrhythmia and for return to sinus rhythm on decreasing the perfusion pressure.

Figure 4

Response of a gas-perfused heart to increased perfusion pressure. Electrogram recorded with electrodes on right atrial appendage and on ventricular apex. The arrows indicate threshold pressure (120 mm Hg) for induction of arrhythmia and for return to sinus rhythm on decreasing the perfusion pressure.

Figure 5

Relationship between resting tension and isometric developed tension in hearts perfused first with Krebs solution and then with gas. Heart rate was 180 beats/min. Regression lines calculated by method of least squares.

Be determined repeatedly in the same heart and was found to remain remarkably constant. The atria did not appear to be affected by the increases in perfusion pressure.

Starling's Relationship

Five hearts, driven electrically at 180 beats/
medium. The procedure was then repeated during gas perfusion. Figure 6A shows a characteristic series of curves obtained in 1 heart. Except at the smallest and the largest loads used, power output during gas perfusion was approximately 1.5 times that during substrate-free liquid perfusion, whereas power output in the presence of glucose was more than 3 times that in its absence. The results from the entire group of preparations, which differed from each other in weight, have been combined by expressing the power output in terms of the maximum power obtained during perfusion with Krebs plus glucose. Figure 6B shows these “normalized” curves to have the same quantitative relationship to each other.

**METABOLIC STUDIES**

We have studied the tissue content of various metabolites during gas and substrate-free liquid perfusion. A 10-g resting tension was applied to the hearts during these studies and contractility was recorded to ensure that the preparations were similar to those used in the physiological studies. The experiments were terminated by quickly cutting off the ventricles during continued gas perfusion, blotting them and freezing in liquid nitrogen. The control group of hearts was treated in the same manner within 30 sec of removal from the animals. The results are summarized in Table 1.

Table 1 shows that the water content of the control group was higher than that of hearts perfused for a brief period, presumably because their vasculature had not been cleared of fluid. The increase in tissue water due to prolonged perfusion with liquid is well known. Tissue water did not decrease during prolonged gas perfusion, which indicates that adequate humidification of the perfusate and of the environment was achieved in our system.

Tissue glycogen content decreased rapidly during the initial 5 min of liquid perfusion and did not change greatly when liquid perfusion was continued for 2 hours. Gas perfusion for 5 min after 5 min of liquid perfusion resulted in a further significant decrease in glycogen content to a level which remained stable for the next 10 hours. Nonglycogen carbohydrate levels changed in a manner similar to that of glycogen. The short period of gas perfusion produced a similar rapid further fall in the levels of lactate and pyruvate which, however, continued so that their levels in individual hearts were no longer measurable.

**PHARMACOLOGICAL STUDIES**

We determined the response of oxygen-perfused hearts to a number of drugs which were administered in 1 or 5 ml Krebs solution. It was essential that the solution be administered into the perfusion cannula rapidly enough to pass through the coronary vessels as a single bolus. Slow injection caused the formation of multiple gas-liquid inter-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Perfusion</th>
<th>Water content %</th>
<th>Glycogen μmoles/g</th>
<th>Other carbohydrates μmoles/g</th>
<th>Lactate μmoles/g</th>
<th>Pyruvate μmoles/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (0 time)</td>
<td>80.9 ± 1.5</td>
<td>72.4 ± 3.8</td>
<td>47.9 ± 4.6</td>
<td>95.7 ± 7.6</td>
<td>0.16 ± 0.02</td>
</tr>
<tr>
<td>Krebs, 5 min</td>
<td>76.6 ± 0.4†</td>
<td>23.8 ± 2.0†</td>
<td>19.3 ± 1.9†</td>
<td>33.2 ± 4.1†</td>
<td>0.08 ± 0.01†</td>
</tr>
<tr>
<td>Gas, 5 min</td>
<td>76.1 ± 0.3</td>
<td>13.8 ± 0.1†</td>
<td>15.6 ± 1.5</td>
<td>10.6 ± 2.5†</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>Gas, 3 hours</td>
<td>76.3 ± 0.4</td>
<td>13.4 ± 0.5</td>
<td>9.2 ± 0.9†</td>
<td>0.1†</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>Gas, 10 hours</td>
<td>76.8 ± 0.5</td>
<td>13.6 ± 0.1</td>
<td>10.0 ± 0.6</td>
<td>—</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>Krebs, 2 hours</td>
<td>84.3 ± 1.9†</td>
<td>19.6 ± 0.7</td>
<td>17.4 ± 1.8†</td>
<td>9.2 ± 1.9†</td>
<td>&lt; 0.03</td>
</tr>
</tbody>
</table>

Means ± SE, four hearts per group; results calculated per gram dry weight of tissue.

*As glucose equivalents.
†Significantly different (P < 0.05) from preceding group and control.
‡Pooled sample.
Top, effect of various loads on the power output of 1 heart perfused with Krebs plus glucose, substrate-free Krebs solution, and gas. Heart rate was 180 beats/min. Bottom “normalized” curves for 4 hearts treated as above. Power output of each heart is expressed as percent of maximum obtained during perfusion with solution containing glucose.

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faces which would not pass through the heart at the usual perfusion pressure.

Injections of Krebs solution resulted in a transient (less than 20 sec) increase in contractility of approximately 10%. There was no change in heart rate. Epinephrine and nor-epinephrine (0.1 to 0.5 μg) increased contractility and rate by 50 to 150%. Dose-response curves were determined for isoproterenol in 4 hearts. This amine was 10 times more potent than epinephrine, a dose of 0.05 μg, producing 50% of maximal increase in contractility. The durations of action of these sympathomimetics were not increased over those produced by similar injections into liquid-perfused hearts. This is probably due to the rapid decomposition of the amines at the high oxygen tensions, although uptake into tissue storage sites cannot be discounted.

The stimulus voltage of driven preparations was increased to 10× threshold in order to determine the response of the gas-perfused heart to release of endogenous catecholamines (18). Figure 7A shows the positive inotropic response to this procedure. The magnitude and duration of the response were potentiated by the prior administration of 1 μg of cocaine (Fig. 7B). Pronethalol (1 to 10 μg), administered after washing out the cocaine by brief perfusion with Krebs solution blocked this response (Fig. 7C). Figure 7D shows that prior treatment of an animal with reserpine makes the gas-perfused heart unresponsive to increases in driving voltage.

**Discussion**

The question arises whether the capillary circulation is perfused by the gas mixture or whether the heart remains viable because oxygen passing through the open left ventricular cavity diffuses into the tissue. We cite the following evidence against the latter possibility:

(A) Although we can observe the escape of gas from the slit in the free wall of the left ventricle, the resistance of the system provides an argument against this being the only route of egress of gas. In a number of experiments the aortic valve opened suddenly, apparently spontaneously; this resulted in a precipitous fall in perfusion pressure and a decrease of 80 to 100% in the force
of contraction of the heart. These preparations could often be restored by gentle manipulation of the left ventricle. Contractility returned to normal together with the return of perfusion pressure. We have also found that slitting of the ventricle is a convenient, rather than an essential, aspect of the preparation.

(B) Cardiogreen dye or diluted india ink (5 ml) were injected through the aortic cannula into several hearts after 2 to 6 hours of gas perfusion. This volume of solution passes through the hearts in 20 to 30 sec. Dissection showed that most or all of the muscle mass had been stained. The exact distribution of dye was somewhat variable, however, small portions of the free walls of the ventricles sometimes showing only light pink coloration.

(C) Although our preparation has maintained contractility for periods longer than those reported by other workers, it is not unique. Dog hearts have been kept alive in vitro and in situ either by orthograde or by retrograde perfusion of the coronary vasculature with gaseous oxygen. Camishion et al. (19) have shown that tissue oxygen tensions, measured with embedded oxygen electrodes during retrograde perfusion, exceed those observed during perfusion with blood. Talbert et al. (4) showed that gas flows of 700 to 1,500 ml/min at pressures of 20 to 50 mm Hg are required during retrograde perfusion. Sabiston et al. (3) measured flows of 300 to 1,000 ml/min at 80 to 120 mm Hg during orthograde perfusion. These flows were observed under conditions where gas escape was impossible. We conclude that gas will flow through the coronary vasculature at reasonable pressures if perfusion with a saline medium precedes gas perfusion and the formation of bubbles is studiously avoided. However, none of the studies, including our own, presents definitive evidence that gas flow occurs through capillary beds.

Gas-perfused hearts beat more strongly, perform more work and fail much more slowly than do hearts perfused with substrate-free Krebs solution. There are several possible reasons for this. It is immediately apparent that the oxygen content, but not necessarily the Po2 of the perfusing medium, is greatly increased during gas perfusion. Lentini (20) reported that the optimal oxygen tension for isolated heart tissue is 700 mm Hg, a partial pressure exceeded in our liquid perfusate. Fisher and Williamson (21) and Opie et al. (22) showed that the oxygen content of liquid perfusates is sufficient to support metabolism in hypodynamic preparations. This may not be true in hearts which are performing work. Blinks and Koch-Weser (23) concluded that the oxygen carrying capacity of liquid perfusates is not sufficient to permit maximal working capacity. Our experiments support their contention by showing that gas perfusion allowed a small increase in work capacity. No definite conclusion can be reached until a method is found to measure the oxygen consumption of hearts perfused with gas. However, maximal work production during oxygen perfusion was only 60% of that obtained when glucose was added to the liquid medium, showing clearly that the major determinant of work capacity is not oxygen content. This confirms the experiments of Neely et al. (24). The possibility that high oxygen may exert a direct pharmacological effect on cardiac contractility cannot be eliminated.

Another reason for better performance could have been a qualitative or quantitative change in the pattern of substrate utilization. Both gas- and liquid-perfused hearts lost most of their carbohydrate stores within 15 min of isolation, indicating that there are no gross changes in the rate of metabolism of these stores. By analogy with the observations of Shipp et al. (25), it would appear probable that gas-perfused hearts derive the energy for contraction from the oxidation of lipids. We are now studying the lipid metabolism of these preparations.

The better performance of gas-perfused hearts may be related to the unique nature of this preparation, in which the extracellular fluid does not equilibrate with a circulating fluid but comes to at least partial equilibrium with the intracellular space. It is possible
that the accumulation in the extracellular fluid of nonvolatile substances lost from the intracellular space may help to maintain contractility. Adenosine and its phosphorylated derivatives, certain lipids, and metabolic cofactors such as nicotinamide have all been shown to be lost into the perfusing medium \((6, 26, 27)\). These substances are all known to have, in higher concentrations, positive inotropic effects on the heart \((28, 29, 30)\). Catecholamines also are lost in the perfusing medium \((31)\), but our experiments showing that injected catecholamines act for only brief periods and the observation that a beta-receptor blocking agent has no negative inotropic effect, appear to eliminate catecholamines as essential for maintained contractility. Preliminary experiments have shown that a new steady-state level of extracellular sodium and potassium ions is achieved within 2 hours of beginning gas perfusion. We have not as yet eliminated the possibility that the increase in contractility during this period is due to the limitation on the net inward diffusion of sodium or outward diffusion of potassium ions. We believe that the observed ability of the gas-perfused heart to maintain contractility for long periods may result in an interesting approach to the problem of cardiac failure.

The gas-perfused heart may lend itself to a variety of other specialized studies of cardiac function. Drugs or other materials may be administered with the assurance that they and their metabolites are not being removed from the preparation by the perfusate. Quantitative recovery of administered vehicle allows estimation of the material retained in the tissue. We cannot be sure, however, that gas-perfused tissue handles drugs in exactly the same manner as do tissues bathed or perfused with liquid.

The absence of substrates in liquid perfusates lowers the threshold for induction of arrhythmia in isolated hearts \((32)\). The gas-perfused heart has a lower threshold than the substrate-free, liquid-perfused heart for the arrhythmia induced by increasing the perfusion pressure. Pressure must exert its effect via the coronary vasculature, since both ventricular cavities are open to the atmosphere. This supports the work of Mainwood \((33)\) and of Panisset et al. \((17)\). Our preparation is of particular interest because pressure-induced changes in rhythm may be reproduced at will and occur at a constant threshold pressure. It may be of interest to study the effects of vasoactive versus cardioactive drugs on these arrhythmias.

The preparation may also be useful in the study of mechanical alternation which is not secondary to arrhythmia or to the action of pharmacological agents. It should be noted especially that alternation occurred in our preparations during the phase of increasing total contractility and was maintained throughout the remainder of the experiment.

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