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Research Article

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Therapeutic interventions were performed in animals having the same degree of ischemia as Group II. Systemic procaine amide in Group III interrupted the tachycardia and egress of K^+, despite persistent ischemia. Group IV did not respond to intracoronary insulin with K^+ uptake, as did normal dogs, and progressed to fibrillation. During the production of hyperglycemia in Group V, myocardial loss of K^+ ceased with maintenance of sinus rhythm. Hemodynamic factors did not appear to have a major role in the genesis of the arrhythmia.

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Abstract. To assess the relation of ventricular arrhythmias to myocardial K^+ movement during ischemia, we placed an electrode catheter in the left anterior descending coronary artery for thrombus production in intact anesthetized dogs. ^{85}Kr injections distal to the thrombus permitted serial coronary blood flow measurements. Animals of Group I with a moderate flow reduction exhibited no arrhythmia or myocardial egress of K^+. In Group II, marked flow reduction was accompanied by an injury potential and loss of K^+ from the ischemic site, before and during ventricular tachycardia.

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Since intracoronary infusion of K^+ in normal dogs similarly altered repolarization and produced fibrillation, it would appear that during ischemia egress of K^+ before development of the arrhythmia indicates a major role of the ion in pathogenesis. This view is supported by the myocardial loss of K^+ and arrhythmia induced in normal dogs by strophanthidin and by the fact that pharmacologic regulation of K^+ loss is associated with correction of the arrhythmia, despite persistence of low blood flow.

Introduction

Ectopic pacemaker activity is one of the major consequences of substantial reduction in coronary blood flow. Continued interest in the possibility of controlling ventricular arrhythmias during ischemia has made it desirable to analyze some of the factors contributing to their pathogenesis. Whereas hypoxia is known to produce a net loss of potassium in the heart muscle (1–3), the degree of blood flow reduction necessary to produce this effect and the temporal relation of the ionic alteration to ventricular arrhythmias have not been established. Hence, we have undertaken examination of the net movement of this ion in the

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ischemic myocardium during coronary artery thrombosis to assess the relation of ion loss to the development of ventricular tachycardia and to the efficacy of various modes of arrhythmia correction.

Methods

Male mongrel dogs, 19–22 kg, were anesthetized 18 hr postprandial with morphine sulfate, 3 mg/kg, and pentobarbital (Nembutal), 12 mg/kg, and studied without opening the chest. After insertion of an endotracheal tube, respiration was regulated with a Harvard respiratory pump (Harvard Apparatus Co., Inc., Dover, Mass.), which facilitated the maintenance of arterial oxygen saturation and pH in the normal range. Catheters were placed in the coronary sinus, aorta, and left ventricle for blood sampling and pressure determinations and in the left coronary artery for myocardial blood flow measurements. Although the catheters were initially filled with dilute heparin, their patency was maintained by slow saline infusions or intermittent flushes during the experiment.

A closed-chest preparation was used for production of coronary artery obstruction, to utilize its greater hemodynamic stability. An electrode catheter was placed in the left anterior descending coronary artery to permit passage of current to effect thrombus formation in a group of anesthetized dogs (4). In a modification of this method, a stainless steel wire electrode was passed through the proximal side hole of a No. 8 Sones-type catheter (U. S. Catheter Co., Glens Falls, N. Y.); the wire electrode encircled the catheter at this level. Measurement of coronary blood flow to the ischemic area was obtainable by injections of ^{85}Kr distal to the thrombus site (Fig. 1). This inert gas method appears to give valid flow measurements over a wide range of tissue perfusion (5, 6). In some animals catheter placement itself was associated with reduction of coronary blood flow, a transient phenomenon in the animals reported here, with blood flow values returning to the normal range before initiation of 200–400 μa of current. Approximately 100 μc of ^{85}Kr was injected at 6–10-min intervals before ischemia and 12–20-min intervals thereafter. Decay slopes were obtained by precordial scintillation counting and background radioactivity was subtracted in the usual manner from the curve derived by precordial counting (5). For the purpose of estimating the size of the ischemic site, Evans blue dye was injected via the coronary artery catheter into the area of ischemia at the conclusion of each experiment, and the dyed tissue was weighed. Thrombus formation was confirmed at postmortem and arterial obstruction appeared to be complete, except in the group of animals with moderate ischemia and no arrhythmia (Group I).

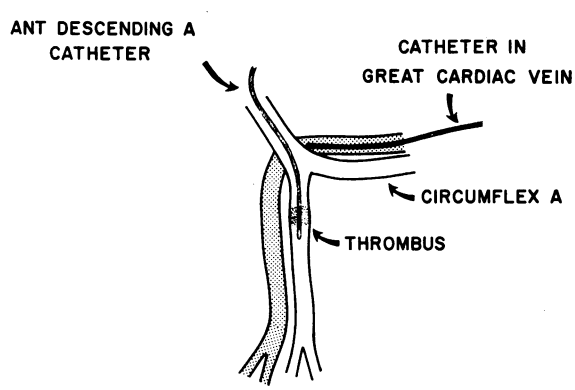

FIG. 1. CATHETER POSITIONS IN CORONARY VESSELS. This diagram demonstrates the position of the electrode catheter in the left anterior (*ANT*) descending coronary artery (*A*) and of the Goodale-Lubin catheter in the great cardiac vein. ^{85}Kr in saline was injected distal to the thrombus site for measurements of blood flow in the ischemic site.

Collection of blood samples from the venous effluent of the ischemic site during obstruction of the anterior descending artery required placement of a coronary sinus catheter under fluoroscopic control into the great cardiac vein (7). Confirmation of the relation of this sampling site to the area of reduced blood flow was obtained by retrograde venous injection of ^{85}Kr during ischemia into the area subserved by the left anterior descending artery. This manner of blood flow measurement gives values closely corresponding to flow values derived by a prior or subsequent arterial injection of this gas (8). Paired sampling of arterial blood and venous blood from the great cardiac vein began with the onset of blood flow reduction at 5-min intervals, for up to 90 min. Net ion movement was calculated from the product of coronary plasma flow and the arterial-coronary sinus (A-CS) difference of K^+ in those animals whose coronary blood flow and arterial ion concentration remained relatively constant, within the 12% error of the flow method and 3% for ion analysis. After flow reduction to a new plateau, the steady-state level was presumably achieved in a short time, in view of the 45 sec duration of the longest transit time in the canine heart (7). Animals that developed hypotension were excluded from our study.

Since the electrocardiographic (EKG) changes occurring in our study during ischemia may be attributable to an altered transcellular distribution of K^+ ion in the heart, potassium chloride in Ringer's solution was infused through a catheter in the left anterior descending coronary artery in a group of normal animals, while the EKG was monitored. Potassium was administered for up to 30 min at a rate of 17 μEq/min in six animals, and 50 μEq/min in another five experiments. The rapid transfer of this ion between coronary plasma and interstitial fluid (9) enabled a relatively constant venous concentration to be achieved in 5–10 min. Plasma samples were taken from the great cardiac vein and aorta for K^+ analysis. A small polyethylene tube within the Sones catheter permitted delivery of this solution to the myocardium, while ^{85}Kr in saline was injected through the outer lumen for blood flow determinations.

In a period of potassium loss from the myocardium during ischemia, elevation of K^+ concentration in coronary venous plasma may result in ion uptake by red cells, with consequent reduction of plasma values. We examined this question using animals that received the lower rate of potassium infusion into the coronary artery. Red cell concentrations were analyzed to assess whether increments in coronary venous plasma produced altered erythrocyte values. In the presence of a coronary venous plasma K^+ rise of 0.74 ± 0.08 mEq/liter, the venous erythrocyte K^+ was 9.22 ± 0.62 mEq/liter compared to red cell samples from the aorta of 9.25 ± 0.58 mEq/liter. These red cell values did not differ from the preinfusion concentrations. Hence, the venous plasma concentration increments seen in the studies of ischemia are unlikely to be affected by the presence of erythrocytes.

To examine the relation of K^+ transfer during attempted arrhythmia correction, we assessed arteriovenous differences after administration of procaine amide, 10 mg/kg i.v. for 60 sec, in an attempt to restore sinus node rhythm. A ventricular ectopic rate of at least 30 beats/min was required before drug usage, since spontaneous restoration of rhythm was not observed in untreated animals who achieved this ectopic rate. Drug efficacy was also evaluated in additional animals in whom technical problems precluded electrolyte studies. Since insulin promotes K^+ uptake in muscle (10), glucagon-free insulin,[1] 40 mU/min, was infused into the left anterior descending coronary artery for 25 min in a group of normal dogs and in animals with an ischemic arrhythmia. In addition, a group of animals was studied after induction of hyperglycemia by infusion of 10% glucose, 40 mEq of KCl, and 20 U of crystalline zinc insulin. After marked coronary blood flow reduction, 500 ml of solution was delivered via the femoral vein, with a priming dose of 12 ml/min for 5 min and 8 ml/min for 55 min. The potassium salt was used to maintain arterial concentrations of this ion at a constant level. Arterial blood glucose concentrations were determined on an autoanalyzer (11).

To elaborate the role of potassium egress in the production of ventricular arrhythmias arising in the absence of ischemia, we induced digitalis toxicity in a separate group of eight animals with acetyl strophanthidin,[2] 0.05 mg/kg, given into a femoral vein over a period of 30 sec. Another seven animals received procaine amide, 10 mg/kg, as well as acetyl strophanthidin. The antiarrhythmic agent was infused 5–10 min before the administration of strophanthidin in view of the rapid onset and short duration of ectopic beats after the latter drug. Both groups underwent prior cervical vagotomy to minimize changes in heart rate. A-CS blood samples were taken at 1 min intervals after strophanthidin and coronary blood flow was measured by the ^{85}Kr method with injection every 3 min.

[1] Donated by Dr. W. R. Kirtley of Eli Lilly & Company, Indianapolis, Ind.

[2] Donated by Dr. G. C. Chiu of Eli Lilly & Company, Indianapolis, Ind.

Plasma potassium was analyzed on a Beckman B spectrophotometer (Beckman Instruments, Inc., Fullerton, Calif.) with a flame attachment. Only samples without significant hemolysis were used. Duplicate determinations for blood oxygen were performed by spectrophotometric assay (12) on arterial and coronary venous samples taken during blood flow measurement. Arterial pH was determined on a Beckman meter at 37°C and hematocrit by the glass capillary method. Donor animals were used for 15-ml blood replacements after each A-CS sampling, procedure which had no apparent effect on ion extraction or hemodynamics in the control observations.

Epicardial EKG from saline-filled coronary arterial and venous catheters were monitored for evidence of injury potentials and left ventricular pressures were examined for contractility changes. An index of contractility change was deduced from the relation of the maximum rate of left ventricular pressure rise to the end diastolic pressure (13–15). Ventricular and femoral arterial presures were measured through 50-cm Goodale-Lubin (U. S. Catheter Co., Glens Falls, N. Y.) 8F catheters connected directly to Statham strain gage transducers (P23Db, Statham Instruments Inc., Los Angeles, Calif.). Intermittent photographic recordings were made from a multichannel oscilloscope recorder (Electronics for Medicine, Inc., White Plains, N. Y.). The first derivative of the left ventricular pressure pulse (dp/dt) was computed by an R-C differentiating circuit and converted into millimeters of Hg per second (15). Ventricular diastolic pressure was recorded at sufficient sensitivity so that 1 mm Hg equaled 5 mm of paper. Measurements were made at the end expiration phase of the respiratory cycle. Statistical variations are expressed as SE and the Student t test was paired (16).

Results

Evidence of coronary artery obstruction occurred 20–90 min after introduction of current in the electrode catheter. Two types of responses to thrombus production were observed, apparently dependent on the degree of coronary blood flow reduction. In animals of Group I (Fig. 2) a moderate flow reduction to 35–55% of control levels was associated with slight ST depression on the epicardial EKG, which was verified in the open-chest preparation at the conclusion of the experiments. Total left ventricular contractility was not significantly affected (Table I). There was no evidence of significant potassium ion egress from the myocardium during the 90 min of electrolyte study and we observed no arrhythmia up to the end of the experiment, 4 hr after the onset of ischemia.

On the other hand, when coronary blood flow was reduced to 15–30% of the control values

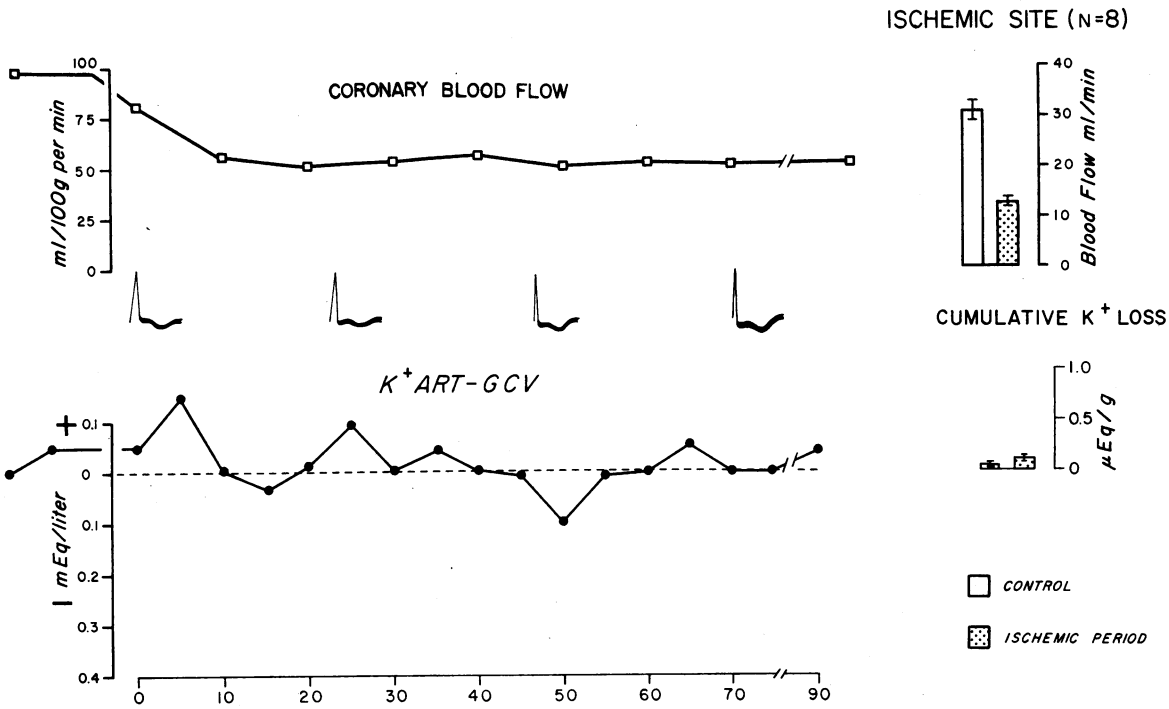

FIG. 2. EFFECTS OF MODERATE CORONARY BLOOD FLOW DECREMENT. The top panel illustrates in an individual animal the moderate decline of coronary blood flow and the minimal ST segment change. The mean blood flow values for the group are depicted in the columns to the right. Below, the negligible differences in the arterial (*Art*) and great cardiac vein (*GCV*) concentrations of K^+ are exhibited. The mean cumulative ion uptake values in the myocardium for the animals of Group I are presented in the columns to the right. The statistical variations are expressed as SE in this and subsequent figures.

(Group II), there was clear evidence of altered repolarization with the appearance of an injury potential on the epicardial lead (Fig. 3). Associated with these changes, increased amounts of potassium ion appeared in the coronary venous effluent draining the ischemic site. This was followed by the appearance of ectopic activity, typically in the form of isolated ventricular extra-

TABLE I

Hemodynamic and myocardial O_2 uptake during ischemia

	Group*									
	I		II		III		IV		V	
	C	E	C	E	C	E	C	E	C	E
LV dp/dt max *mm Hg/sec* ±	2650 32	2595 27	2725 38	2069‡ 29	2800 41	2155‡ 37	2550 53	1975‡ 47	2590 44	2210§ 58
LV end diastolic pressure ±	7.2 0.8	7.8 0.9	6.3 0.4	11.5‡ 1.0	5.9 0.3	10.8‡ 0.9	7.5 0.7	12.3‡ 1.1	6.1 0.5	11.4‡ 1.2
Heart rate/min ±	148 9	153 11	132 12	121 12	136 8	139 13	141 12	148 9	128 8	125 12
Aortic pressure mean, *mm Hg* ±	114 11	109 9	111 6	114 8	117 7	116 6	115 9	108 8	112 5	114 7
Myocardial O_2 uptake, *ml/100 g per min* ±	12.9 0.62	6.9‡ 0.42	12.1 0.78	3.7‡ 0.21	13.2 0.85	3.9‡ 0.28	12.6 0.69	4.2‡ 0.37		

C, Control; E, value obtaining at time of maximum change during ischemia before ectopic beats, except Group V, which represents value at end of infusion; LV, left ventricular.

* Group I, no ventricular arrhythmia; II, ventricular arrhythmia without therapy; III, ventricular arrhythmia with procaine amide; IV, ventricular arrhythmia with insulin; V, glucose infusion begun before anticipated arrhythmia.

‡ Statistically significant at $P < 0.01$ in paired t test.

§ Significant at $P < 0.05$.

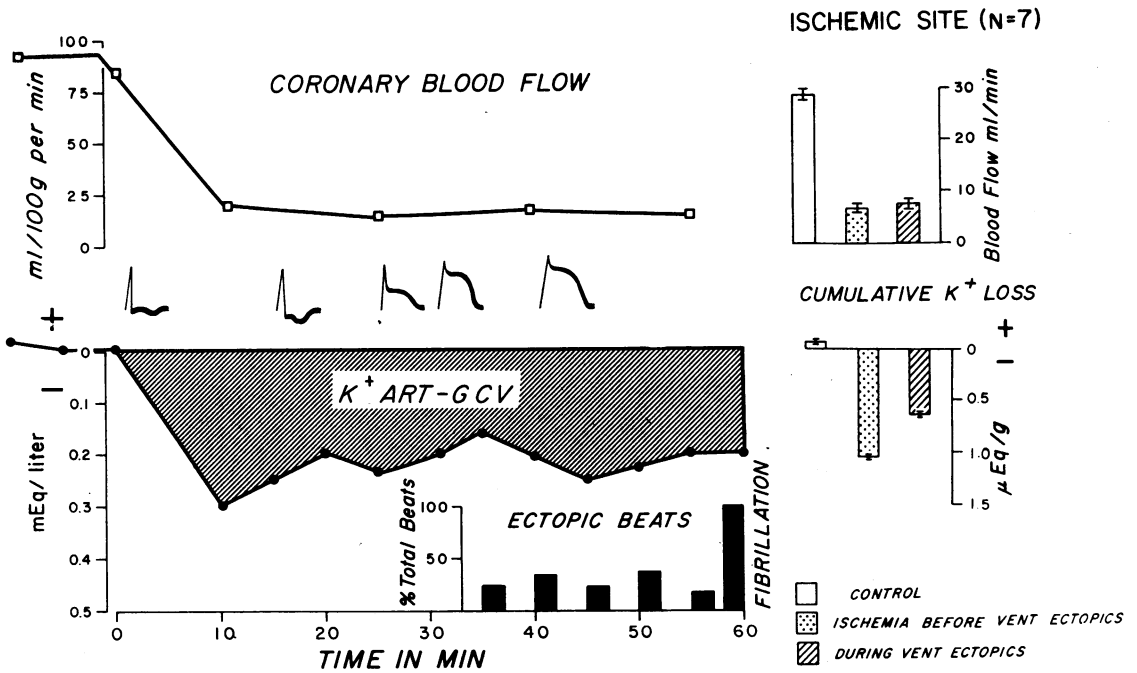

FIG. 3. EFFECTS OF MARKED CORONARY BLOOD FLOW DECREMENT. The course of ischemia in an individual animal of Group II is indicated in the upper panel while the mean blood flow for the group before and during the appearance of ectopic beats is depicted in the columns to the right. The lower panel indicates the time course of K^+ loss from the myocardium, reflected in the negative arteriovenous differences in the presence of constant arterial levels of the cation. An injury potential ensues, as seen in the middle of the figure, after the onset of ventricular (*vent*) ectopic beats at 35 min of ischemia, which progressed to tachycardia and fibrillation. Whereas the calculated K^+ loss for the period of ventricular ectopics is less than in the preectopic period as seen in columns to the lower right, this difference becomes insignificant when adjusted for the shorter duration of the ventricular ectopic period.

systoles, which increased in frequency until a ventricular tachycardia developed. This degree of coronary blood flow reduction culminated in ventricular fibrillation in all untreated animals.

In view of the association of K^+ egress with the EKG manifestations of ischemia, KCl was infused into the anterior descending artery of normal animals (Table II). A continuous infusion of potassium, 17 μEq/min, into the left coronary artery of six animals produced a steady-state K^+ increment of 0.74 ± 0.08 μEq/liter in the coronary venous plasma within 6 min and was associated

TABLE II

Intracoronary infusion of potassium chloride

Dosage of K^+/min		Time of steady-state* concentrations	K^+ in GCV‡	EKG	Coronary blood flow
		min	*mEq/liter*		*ml/100 g per min*
	C§		4.28 ± 0.04	Normal	97 ± 3
17 μEq, n = 6	E	6	5.02 ± 0.08	ST segment elevation	95 ± 4
	C		4.19 ± 0.06	Normal	94 ± 6
50 μEq, n=5	E	10	6.41 ± 0.11	Ventricular tachycardia	96 ± 5‖

* Maximum time in the group of animals for appearance of constant concentrations in the coronary vein.
‡ Great cardiac vein.
§ C, represents control values; E, represents data during experiments with potassium infusion.
‖ Coronary blood flow before arrhythmia.

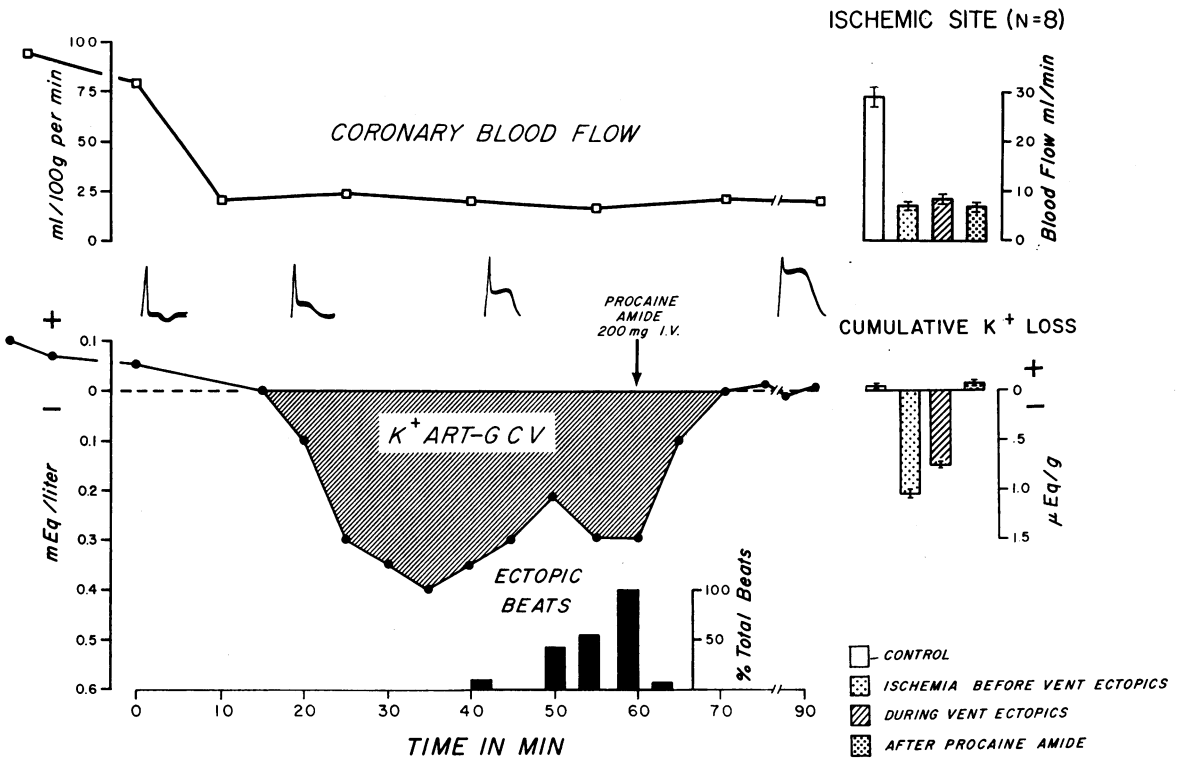

FIG. 4. POTASSIUM EGRESS AND PROCAINE AMIDE. The course of ischemia in an individual animal receiving procaine amide illustrates, from top to bottom, coronary blood flow, the injury potential, alterations in myocardial K^+ transfer, and the incidence of ectopic beats before and after the drug. The columns to the right indicate the persistent blood flow reduction in this group after procaine amide (above), but a definite reduction in K^+ loss from the myocardium (below).

with significant elevation of the ST segment. At an infusion rate of 50 μEq/min in five experiments, after ST alteration, ventricular ectopic beats and fibrillation were produced at coronary venous concentrations of 2.2 ± 0.11 μEq/liter. The terminal arrhythmia occurred between 10 and 15 min after the onset of infusion. No significant change of coronary blood flow or systemic arterial potassium concentration was observed in either group.

To assess the influence of procaine amide on the course of ischemia, we studied another group (III, Fig. 4) that had a degree of coronary blood flow reduction, injury potential, and loss of potassium ion similar to that of Group II. After the development of ectopic beats and ventricular tachycardia, the introduction of the antiarrhythmic agent procaine amide, 10 mg/kg i.v., effected a reduced frequency of ventricular ectopic beats and disappearance of the ventricular arrhythmia usually within several minutes. With the exception of two animals who required repetitive doses, normal sinus rhythm was maintained until termination of the experiment about 3 hr after the initial drug usage. Associated with this therapeutic response was a decline in the egress of potassium from the heart without detectable alteration of blood flow. The reduction of ion loss in the 30 min after administration of drugs was highly significant when compared with that in the pretreatment period ($P < 0.001$). The surviving animals treated with procaine amide had a blood flow reduction during development of the arrhythmia similar to that of the untreated animals that fibrillated. The cumulative potassium loss calculated from the product of flow and negative arteriovenous differences revealed that a similar amount of ion was lost during the period from the stable blood flow reduction to the appearance of ectopic beats in the treated and untreated animals.

A different time course was observed in nine animals that are not included in Group III because

the rapid appearance of ventricular tachycardia within a minute after the initial ectopic beat precluded study of ion transport. These animals, with one exception, were unresponsive to procaine amide. 12 of 13 animals with the less abrupt course, averaging 26 min, were restored to normal sinus rhythm after use of this drug.

The sustained infusion of insulin into the left anterior descending coronary artery of normal animals resulted in a substantial uptake of potassium ion over the course of hormone infusion, without alteration of arterial concentrations (Fig. 5). In ischemic Group IV, infusion of hormone into the hypoxic site after the onset of ventricular ectopic beats and potassium loss from the myocardium produced no effect on ion egress, and fibrillation ensued. In none of the six animals so treated was significant antiarrhythmic activity observed. In contrast, during the systemic infusion of glucose with insulin and potassium in ischemic Group V (Fig. 6), there was an early reversion of the myocardial K^+ release. The production of hyperglycemia was attended by rapid reduction of the K^+ loss already underway, followed by a period of uptake of this ion. The change in cumulative ion movement observed in this circumstance was significantly different from that of Group II ($P < 0.01$). No significant ectopic activity occurred despite the persistence of the same degree of coronary flow reduction.

As a possible important variable during the response to hypoxia, the weight of the ischemic area did not significantly differ in these studies. In Groups I, II, III, IV, and V the weights were 35.3 ± 1.2, 36.1 ± 1.8, 34.8 ± 1.4, 34.4 ± 1.2, and 35.9 ± 1.7 g, respectively.

In assessing myocardial K^+ transfer during the production of ectopic beats in the absence of ischemia, we found that administration of acetyl strophanthidin, 0.05 mg/kg, produced prompt egress of K^+ from the normal left ventricle before the onset of a ventricular arrhythmia, which ap-

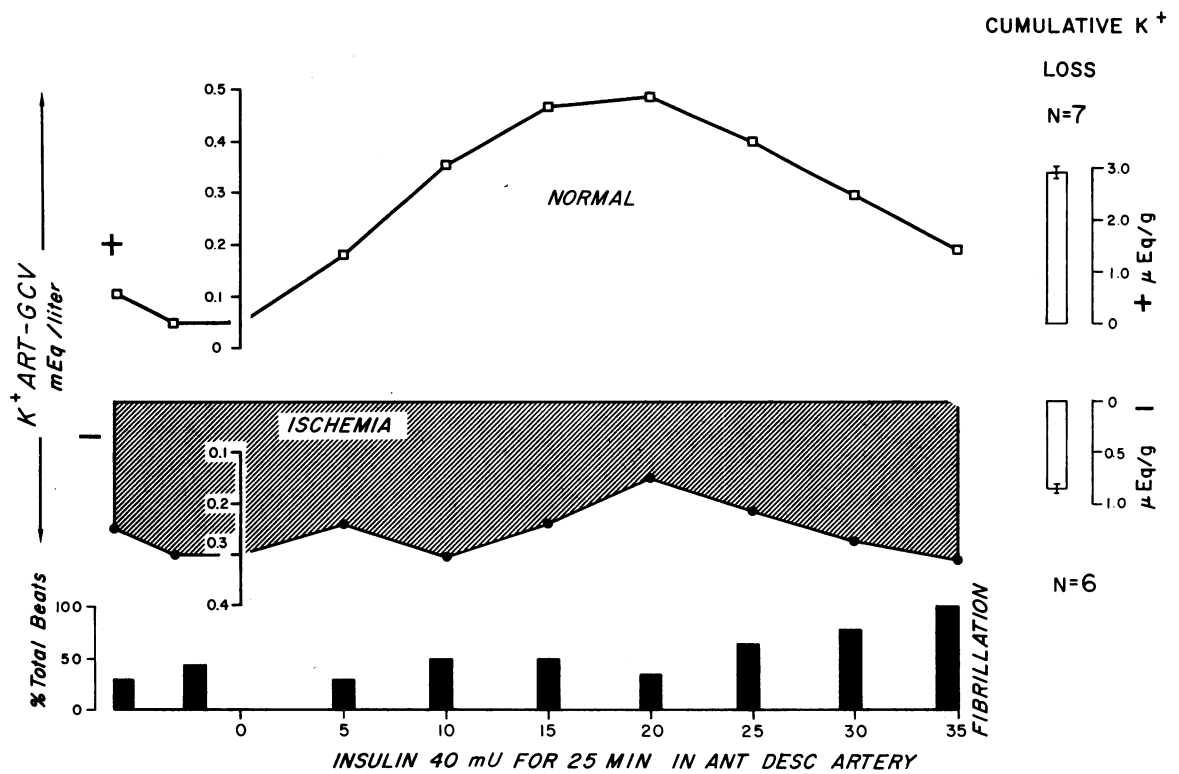

FIG. 5. POTASSIUM EGRESS AND INSULIN. The change in myocardial extraction of K^+ in normal animals is illustrated in the top panel. The response to insulin in ischemic animals (Group IV) is seen below, with the time course of an individual experiment. The cumulative K^+ change for the normal (above) and ischemic animals (below) is indicated in the columns to the right. *Ant Desc,* anterior descending; *GCV,* great cardiac vein.

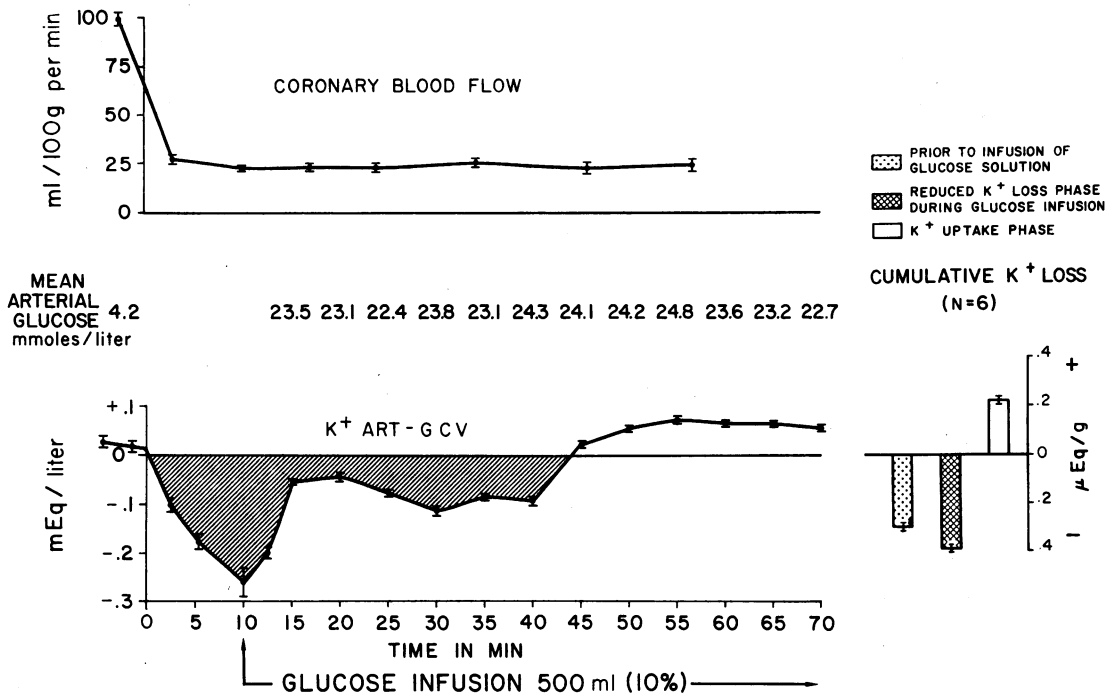

FIG. 6. EFFECTS OF INFUSION OF GLUCOSE SOLUTION ON K^+ TRANSFER DURING ISCHEMIA. Coronary blood flow (top panel) remained at ischemic levels in Group V during the infusion of 500 ml of 10% glucose, 40 mEq of KCl, and 20 U of insulin, beginning after 10 min of ischemia which increased arterial concentrations sixfold (middle of figure). The bottom panel indicates the time course of the reversion of the K^+ loss consequent to ischemia in this group of six animals. The columns to the right indicate the cumulative ion loss during the initial 10 min of ischemia, the cumulative loss during the first 30 min of glucose infusion indicating a reduced rate of loss, and the subsequent uptake of K^+. In contrast to the animals of Group II, none developed ventricular tachycardia and fibrillation despite a similar reduction of coronary blood flow.

peared in each animal between 3 and 4 min after injection (Fig. 7). At the peak of toxicity the majority of beats were ectopic. The gradual, spontaneous restoration of normal sinus rhythm was associated with disappearance of significant ion loss from the myocardium. In another group of animals, pretreated with procaine amide 5–10 min before infusion of strophanthidin, toxicity was avoided in the presence of a significantly reduced loss of potassium.

The cumulative K^+ loss from the myocardium was calculated as the product of coronary plasma flow and the arteriovenous difference of this ion. In the ischemic animals that developed an arrhythmia (Groups II and III, Fig. 3 and 4), the K^+ egress up to the appearance of ectopic beats was approximately 1 μEq/g of ischemic tissue. A similar value was derived in the animals receiving toxic doses of strophanthidin (Fig. 7), by extrapolating a value for the 1st min from the 2nd and 3rd min back to control values. In the latter group this degree of ion loss was achieved in about one-seventh the time of the ischemic group because of the larger concentrations of K^+ in coronary venous blood and the presence of normal coronary plasma flow.

The hemodynamic alterations in these five groups of animals are summarized in Table I. There was no significant change from the control period in the two major determinants of coronary flow (17), arterial pressure, and heart rate, during the initial phase of ischemia. Also, during the course of the ectopic rhythm, heart rate was not significantly changed from the relatively high control values. Exceptions occurred only just before ventricular fibrillation. The animals of Group I with a moderate coronary blood flow reduction did not have a significant elevation of left ventricular end diastolic pressure or diminished dp/dt max, despite a significant decline in O_2 consumption at the ischemic site. Left ventricular contractility appeared diminished in Groups II, III, and IV

before the onset of ventricular tachycardia. An apparently similar decline of function was seen in Group V in which no arrhythmia occurred. Groups II, III, and IV exhibited a similar O_2 extraction increase and a myocardial O_2 consumption reduction to about 30% of control, associated with the marked coronary flow reduction.

Discussion

Our studies have indicated that ventricular ectopic beats eventuating in fibrillation can occur without complete cessation of coronary blood flow. Those animals with apparently complete coronary artery obstruction presumably had significant collateral flow available from the circumflex artery, as has been demonstrated during ligation of the anterior descending artery (18). Nevertheless, severe hypoxia was sufficiently present to produce fibrillation. The absence of significant ectopic beats, in the presence of a less severe flow reduction to 35–55% of control, indicates that a degree of hypoxia may be tolerated for at least several hours as previously suggested (19), if not for an indefinite period.

There were no significant alterations of heart rate and arterial pressure up to the time of development of ectopic beats, which might have contributed to the genesis of the arrhythmia. Depressed contractility during marked ischemia would also not appear to be an important determinant of abnormal electrical impulse formation, since a similar alteration in left ventricular pressures was observed in the animals receiving the glucose solution without an arrhythmia, as was found in the groups developing ventricular tachycardia.

Altered ventricular repolarization manifest as ST segment elevation occurred only in animals with marked decline in coronary blood flow and a net loss of K^+ from the ischemic myocardium. This electrophysiologic alteration may be related to the abnormal ionic movements induced by severe ischemia. A similar repolarization change was seen during acute elevation of extracellular K^+, in agreement with a prior report (20). Measurements of the transmembrane action potential during hypoxia have also indicated a close similarity to the effects of elevated K^+ in the extracellular fluid (21). In view of the persistence of the ST segment elevation after pharmacologic correction of the net K^+ loss however, either another basis for this electrophysiologic change must exist, or an irreversible alteration has occurred. Although no definitive evidence is available, if there is no net uptake of this ion by the cells after drug

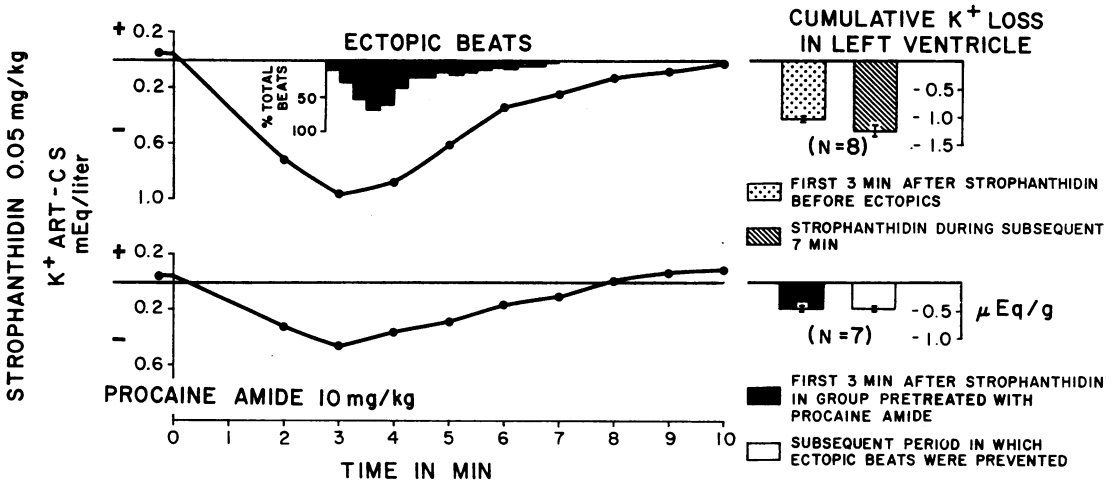

FIG. 7. STROPHANTHIDIN-INDUCED K^+ LOSS, MODIFIED BY PROCAINE AMIDE. The upper panel illustrates the time course of the negative arterial-coronary sinus (*CS*) differences of K^+ in a representative experiment after acetyl strophanthidin given at zero time. Cumulative ion loss, shown in columns to the right, was calculated from the product of the arteriovenous difference and coronary plasma flow of 0.57 ± 0.08 ml/g per min, which was not significantly changed from control. In the lower panel, procaine amide, given 5–10 min before strophantidin, substantially reduced the loss of cation from the myocardium, approximating the smaller ion egress seen after nontoxic doses with positive inotopic activity (10). The mean coronary plasma flow in the treatment group, at 0.5 ± 0.06 ml/g per min, was not significantly changed from the predrug values.

intervention, the continued reduction of the transcellular ratio may contribute to the persistent repolarization change.

The observation that net loss of K^+ from the myocardium antecedes the appearance of ventricular ectopic beats indicates that such ion egress is not a secondary manifestation of the arrhythmia, but may provide a metabolic basis for its origin. The fact that restoration of normal sinus rhythm by procaine amide is attended by reversal of ion loss supports this view. During the course of ineffective therapy with insulin, such reversal was not seen. Further, the production of hyperglycemia during the systemic infusion of a solution containing glucose, insulin, and potassium diminished the elevated coronary venous concentrations of K^+ seen early in the course of ischemia and no ventricular arrhythmia was observed. Persistence of the reduced myocardial blood flow and oxygen consumption after antiarrhythmic therapy indicates that while hypoxia initiated the egress of K^+ ion, control of the latter variable appears to determine the efficacy of pharmacologic intervention, despite the persistence of an unaltered level of hypoxia. Although no other metabolic property is known to be shared by the antiarrhythmic agents used, an effect on cellular swelling or the altered nucleotide metabolism of ischemia, which could mediate the regulation of ion transport, is not excluded.

An inconsistent relationship of coronary venous potassium to ventricular arrhythmias was observed during ischemia in a prior study of open-chest animals (22), whereas a positive relation has been observed in individual animals (23). However the former observations, particularly, were limited by the fact that blood sampling was not frequent enough and the arterial concentrations were not sufficiently constant to interpret arteriovenous differences of K^+ adequately, even if coronary blood flow was stabilized during ischemia. In addition, the coronary venous samples may well have included effluent from normal myocardium.

An important role of the potassium ion in the genesis of ectopic activity is also suggested by findings during the cardiotoxic responses to acetyl strophanthidin and effective antiarrhythmic therapy. Ventricular arrhythmias that immediately follow experimental hypercapnia (24) and appear after the administration of octylamine (25) have been similarly associated with loss of K^+ from the ventricle. In addition, ectopic activity has been observed in the late stages of a sustained infusion of epinephrine, when there is egress of this ion from the ventricle (26).

The relevance of this cation is further evidenced by the production of ventricular ectopic beats during intracoronary infusion of potassium chloride, in accord with previous studies (20, 23). The induction of ventricular ectopic beats and fibrillation by increments of extracellular K^+ suggests that a net outward movement of the ion from the cell is likely to modify rhythmicity principally through its effect on the transcellular ratio. The higher extracellular concentration of K^+, seen during the infusions of this ion which result in ventricular arrhythmias, could still be consistent with a reduced transcellular ratio that approximates the level seen during ischemia or strophanthidin usage. In these latter instances intracellular K^+ loss requires less of a rise outside the cell to produce a given ratio decrement. Moreover, if significant ion accumulation occurs in the interstitial space when blood flow is reduced to about 25% of normal, there may be a greater effect on the ratio than might be anticipated from the coronary venous K^+ concentration. Infusion of potassium chloride, on the other hand, may be associated with cellular uptake of ion, necessitating a larger K^+ increment at the cell exterior to produce a similar ratio reduction.

Arrhythmias resulting from ischemia or excess strophanthidin were both associated with a calculated loss of about 1 μEq/g up to the time of appearance of ectopic beats. Hence, a decrease in the transcellular ratio achieved by the egress of a small percentage of total tissue potassium would appear to be a basis for ectopic activity. Whether the subcellular localization of the ion egress may itself have specificity for modifying the electrical properties of the cell is for further investigation to decide. Available information on the role of other cations during ischemia suggests that the tissue increment of sodium is not equivalent to the K^+ egress and is perhaps not significant for at least the 1st hr of coronary artery obstruction (2). Under conditions of abnormal calcium or hydrogen ion distribution the observed relation of K^+ to rhythmicity could well be modified.

It is noteworthy that the property of insulin responsible for promoting K^+ uptake in the myo-

cardium appears to be substantially altered at normal arterial glucose levels during hypoxia. A similar ineffectiveness has been observed when egress of myocardial potassium was induced by acetyl strophanthidin (10), so that the state of K^+ transport in cardiac muscle may qualitatively modify the hormones' action on ion uptake. In the instance of ischemia, there is a qualitative restoration of the normal response of the cation to insulin during the production of hyperglycemia, associated with antiarrhythmic effects in agreement with an earlier report (27).

The therapeutic refractoriness of ventricular tachycardia to procaine amide, when this arrhythmia occurred rapidly after the onset of ectopic beats, is probably not related to the degree of blood flow restriction in the ischemic site. The coronary blood flow decrement appeared to be at the same level as that seen in animals responding to procaine amide, and in this latter circumstance delivery of drug to the ischemic site was inferred from the interruption of the ionic response to hypoxia. That a relative delay in achieving therapeutic drug concentrations during the rapidly evolving tachycardia is at least a contributing factor is suggested by the greater efficacy of procaine amide, administered as pretreatment, in aborting the ventricular fibrillation that follows release of coronary artery obstruction (28).

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References

1. Conn, H. L., Jr. 1956. Effects of digitalis and hypoxia on potassium transfer and distribution in the dog heart. *Am. J. Physiol.* **184**: 548.
2. Russell, R. A., J. Crafoord, and A. S. Harris. 1961. Changes in myocardial composition after coronary artery ligation. *Am. J. Physiol.* **200**: 995.
3. Cherbakoff, A., S. Toyama, and W. F. Hamilton. 1957. Relation between coronary sinus plasma potassium and cardiac arrhythmia. *Circulation Res.* **5**: 517.
4. Salazar, A. E. 1961. Experimental myocardial infarction: Induction of coronary thrombosis in the intact closed-chest dog. *Circulation Res.* **9**: 1351.
5. Herd, J. A., M. Hollenberg, G. D. Thorburn, H. H. Kopald, and A. C. Barger. 1962. Myocardial blood flow determined with Krypton-85 in unanesthetized dogs. *Am. J. Physiol.* **203**: 122.
6. Ross, R. S., K. Ueda, P. R. Lichtlen, and J. R. Rees. 1964. Measurement of myocardial blood flow in animals and man by selective injection of radioactive inert gas into the coronary arteries. *Circulation Res.* **15**: 28.
7. Friesinger, G. C., J. Schaefer, R. A. Gaertner, and R. S. Ross. 1964. Coronary sinus drainage and measurement of left coronary artery flow in the dog. *Am. J. Physiol.* **206**: 57.
8. Harman, M. A., A. Markov, P. H. Lehan, H. A. Oldewurtel, and T. J. Regan. 1966. Coronary blood flow measurements in the presence of arterial obstruction. *Circulation Res.* **19**: 632.
9. Conn, H. L., Jr., and J. S. Robertson. 1955. Kinetics of potassium transfer in the left ventricle of the intact dog. *Am. J. Physiol.* **181**: 319.
10. Regan, T. J., M. J. Frank, P. H. Lehan, and H. K. Hellems. 1963. Relationship of insulin and strophanthidin in myocardial metabolism and function. *Am. J. Physiol.* **205(4)**: 790.
11. Hill, J. B., and G. Kessler. 1961. An automated determination of glucose utilizing a glucose oxidase-peroxidase system. *J. Lab. Clin. Med.* **57**: 970.
12. Nahas, G. G. 1958. A simplified lucite cuvette for the spectrophotometric measurement of hemoglobin and oxygemoglobin. *J. Appl. Physiol.* **13**: 147.
13. Downing, S. E. 1964. Effects of angiotensin II and norepinephrine on ventricular performance during oligemic shock. *Yale J. Biol. Med.* **36**: 407.
14. Wallace, A. G., N. S. Skinner, Jr., and J. H. Mitchell. 1963. Hemodynamic determinants of the maximal rate of rise of left ventricular pressure. *Am. J. Physiol.* **205**: 30.
15. Reeves, T. J., L. L. Hefner, W. B. Jones, C. Goghlan, G. Prieto, and J. Carroll. 1960. The hemodynamic determinants of the rate of change in pressure in the left ventricle during isometric contraction. *Am. Heart J.* **60**: 745.
16. Batson, H. C. 1957. An introduction to statistics in the medical sciences. Burgess, Publishing Co., Minneapolis. 14.
17. Katz, L. N. 1959. Work and the heart. P. N. Hoeber, New York.
18. Johansson, B., E. Londer, and T. Seeman. 1964. Collateral blood flow in the myocardium of dogs measured with Krypton-85. *Acta Physiol. Scand.* **62**: 263.
19. Wégria, R., M. Segers, R. P. Keating, and H. P. Ward. 1949. Relationship between the reduction in coronary flow and the appearance of electrocardiographic changes. *Am. Heart J.* **38**: 90.
20. Soloff, L. A., G. A. de los Santos, and J. Oppenheimer. 1960. Electrocardiographic changes produced by potassium and other ions injected into the coronary arteries of intact dogs. *Circulation Res.* **8**: 479.

21. Hoffman, B. F., and P. F. Cranefield. 1960. Electrophysiology of the heart. McGraw Hill Book Company, New York.
22. Wexler, J., and H. H. Patt. 1960. Evidence that serum potassium is not the etiological agent in ventricular fibrillation following coronary artery occlusion. *Am. Heart J.* **60**: 618.
23. Harris, S. A., A. Bisteni, R. A. Russell, J. C. Brigham, and J. E. Firestone. 1954. Excitatory factors in ventricular tachycardia resulting from myocardial ischemia; potassium a major excitant. *Science.* **119**: 200.
24. Brown, E. B., Jr., and A. Mowlem. 1960. Potassium loss from the heart during the immediate posthypercapnic period. *Am. J. Physiol.* **198**: 962.
25. Hano, J. E., and A. S. Harris. 1963. Effects of histamine and potassium release agents on ventricular rhythms before and after coronary occlusion. *Am. Heart J.* **65**: 368.
26. Regan, T. J., C. B. Moschos, P. H. Lehan, H. A. Oldewurtel, and H. K. Hellems. 1966. Lipid and carbohydrate metabolism of myocardium during the biphasic inotropic response to epinephrine. *Circulation Res.* **19**: 307.
27. Sodi-Pallares, D., A. Bisteni, G. A. Medrano, M. R. Testelli, and A. De Micheli. 1963. The polarizing treatment of acute myocardial infarction. *Dis. Chest.* **43**: 424.
28. Sommers, H. M., and R. B. Jennings. 1964. The influence of procaine amide and oxygen on the onset of ventricular fibrillation following temporary occlusion of the left circumflex coronary artery. *Federation Proc.* **23**: 444. (Abstr.)