

The Anrep Effect Reconsidered

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ABSTRACT Evidence is presented supporting the hypothesis that the positive inotropic effect after an abrupt increase in systolic pressure (Anrep effect) is the recovery from subendocardial ischemia induced by the increase and subsequently corrected by vascular autoregulation of the coronary bed. Major evidence consists of data obtained from an isolated heart preparation showing that the Anrep effect can be abolished with coronary vasodilation, and that with an abrupt increase in systolic pressure there is a significant reduction in the distribution of coronary flow to subendocardial layers of the ventricle. Furthermore, the intracardiac electrocardiogram shows S-T segment and T wave changes after an abrupt increase in ventricular pressure similar to that noted after coronary constriction. Major implications are that normally there may be ischemia of the subendocardial layers tending to reduce myocardial contractility which may account, in part, for the positive inotropic effect of various coronary vasodilators; that with an abrupt increase in ventricular pressure the subendocardium is rendered temporarily ischemic, placing the heart in jeopardy from arrhythmias until this is corrected; and that end-diastolic pressure and the intracardiac electrocardiogram may provide a means of evaluating the adequacy of circulation to subendocardial layers in diseased ventricles when systolic pressure is abruptly increased.

INTRODUCTION

In 1912 Knowlton and Starling (1) as well as Anrep (2) noted that if left ventricular systolic pressure was

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abruptly increased in a heart lung preparation by increasing resistance to outflow, a positive inotropic effect developed subsequent to the increase, as manifested by a decrease in left ventricular end-diastolic pressure and volume while systolic pressure was maintained constant. As Starling observed this effect to be accompanied by an increase in coronary flow he later attributed it to "improved nourishment of the muscle" (3, 4). In 1959 Rosenblueth, Alanis, Lopex, and Rubio (5) noted that the effect was independent of changes in coronary flow and in 1960 Sarnoff, Mitchell, Gilmore and Remensnyder (6) showed the effect to persist even when coronary flow was maintained constant thereby casting doubt on the hypothesis proposed by Starling.

A thought-provoking review of this phenomenon, termed by Sarnoff and Mitchell the "Anrep" effect (7), was published by Blinks and Koch-Weser in 1963 (8). Essentially, they concluded that the mechanism of the Anrep effect still remained obscure. They, too, dismissed the coronary flow hypothesis of Starling, in view of the findings of Rosenblueth et al. (5) and Sarnoff et al. (6). As the effect was noted in reserpinized preparations (8, 9) they were disinclined to implicate catecholamines in its mechanism. Despite the fact that Sarnoff et al. showed an efflux of potassium from the heart after a sudden increase in systolic pressure (10) Blinks and Koch-Weser pointed out differences between the Anrep effect and the Bowditch effect, making it doubtful that similar mechanisms were involved. Foremost in these differences was the observation that the Anrep effect is not found in cardiac muscle strip preparations (8, 11).

Later, a report from this laboratory showed the effect to be decreased, but not abolished in an isolated heart preparation treated with propranolol (9). Here it was postulated that at least part of the mechanism could be attributed to catecholamines as norepinephrine has been shown to be released by the ventricle in quantities roughly proportional to systolic pressure (12, 13). Ad-

mittedly, however, these authors were unable to ascribe a single mechanism to explain completely the "Anrep" effect (9).

Mindful of the findings of Blinks and Koch-Weser (8) as well as Gilmore, Cingolani, Taylor, and McDonald (11) that the effect is not seen in muscle strip preparations, but only seen in intact hearts, and mindful that coronary flow is not present in muscle strip preparations it was decided to attempt to study, in depth, the interrelationships of coronary flow and the "Anrep" effect using an isolated heart preparation. From these studies evidence was obtained which suggests that the "Anrep" effect, rather than being due to an increased state of contractility or intrinsic adaptation that appears subsequent to an abrupt increase in ventricular pressure (5-11, 14), is more accurately described as the recovery from a negative inotropic effect caused by the abrupt increase. Further evidence was obtained suggesting that subendocardial ischemia is responsible for the negative inotropic effect, a condition which is subsequently corrected by vascular autoregulation of the coronary bed with a redistribution of coronary flow.

This hypothesis, far from being novel, was at least in part implied by Starling and others who used the term "recovery" when describing the effect (2, 3). The object of this report is to present evidence supporting this position and discuss its physiological and clinical implications.

METHODS

The isolated heart preparation. The basic preparation has been described previously in detail (15, 16). Only slight modifications of the original design were made to permit rapid stabilization of systolic pressure. Fig. 1 is a schematic diagram of the modified preparation.

As previously described (15, 16), hearts with lungs attached were excised as quickly as possible from heparinized healthy mongrel dogs weighing 11-25 kg under chloralose (60 mg/kg) and urethane (900 mg/kg) anesthesia. After excision, the hearts were immediately perfused with blood from the femoral artery of a healthy, similarly anesthetized and heparinized, donor dog. As illustrated in Fig. 1, arterial blood from the donor was directed retrograde into the aorta of the isolated heart using a peristaltic pump (Harvard Apparatus Co., Inc., Millis, Mass., model 1215). A Starling resistance was used to maintain the pressure of the perfusing blood constant at approximately 100 mm Hg, and a small (20 ml) air chamber was connected to the aorta to insure a relatively nonpulsatile flow.

With the heart perfused, the pulmonary artery was cannulated and both vena cavae ligated. All coronary venous blood was directed, therefore, through the pulmonary artery cannula and, in turn, through a section of thin walled, compliant tubing ($\frac{3}{4}$ inch Penrose drain). The latter was located 5 cm below the level of the heart and served to dampen the pulsations of coronary venous flow. From there blood was directed to a rotameter (Fischer & Porter Co., Warminster, Pa., 36-541-22) and returned to the donor. Total coronary flow was measured by the rotameter while the

coronary sinus pressure was maintained at a constant, slightly negative pressure.

After cannulation of the pulmonary artery, the pericardium was incised and the right atrium opened. The bundle of His was ligated and electrocoagulated to insure a complete heart block. A selected ventricular rate could then be maintained by electrical stimulation of the distal portion of the ligated His bundle with a pulse generator. Through the opening in the right atrium a plastic covered, stranded, stainless steel wire snare was positioned circumferentially around the outside of the left ventricle and septum at the maximum diameter of the ventricle and maintained in position with loose sutures. As shown in Fig. 1 the snare was mechanically attached to a linear displacement transducer (Hewlett-Packard Co., Waltham, Mass., Linear-syn 585 DT) thereby allowing the transducer to measure the circumference of the left ventricle continuously.

After closure of the right atriotomy a small cardiac catheter (i.d. 1.0 mm) and a large cannula (i.d. 5.0 mm) were inserted into the left ventricle by way of the pulmonary veins. The catheter was attached to a linear differential transducer (Sanborn 267B, Hewlett-Packard Co.) for continuous measurement of left ventricular pressure. The cannula was attached to the Starling resistance shown on the upper right of Fig. 1. By adjusting the pressure applied to the Starling resistance the peak left ventricular pressure could be maintained at a predetermined level.

After perfusion was established and the catheters inserted, the individual pulmonary lobes were ligated at the hilus and removed, and the heart immersed to the level of the coronary ostia in a bath of normal saline maintained at 37°C. Coronary perfusion pressure was monitored at the level of the coronary ostia with a pressure transducer (Sanborn 267B, Hewlett-Packard Co.). In some experiments the intraventricular electrocardiogram was obtained from a bipolar electrode catheter inserted into the left ventricular cavity through a pulmonary vein. The perfusion pressure, ventricular pressure, ventricular circumference and the intracardiac electrocardiogram were continuously recorded on a Sanborn recorder (Sanborn 964, Hewlett-Packard Co.). The surface of the saline in which the heart was immersed provided the reference level for the pressure transducers and was maintained constant by a syphon.

While perfused as described the heart contracted at the stimulated rate. As the Starling resistance containing the coronary venous blood was slightly lower than the heart, the right ventricle was kept empty by a continuous negative pressure. The left ventricle, on the other hand, contracted virtually isovolumically at a constant systolic pressure, ejecting only that small flow that reached the ventricle from the aorta via arterioluminal channels (17). The peak systolic pressure developed by the ventricle was that required to overcome the pressure applied to the Starling resistance shown on the upper right of Fig. 1. The end-diastolic pressure, on the other hand, was an independent variable which served to indicate the inotropic state of the ventricle as it was that which the ventricle required to develop its peak systolic pressure.

To increase systolic pressure abruptly in the experiments subsequently described, the valve shown on the upper portion of Fig. 1 was opened after the upper Starling resistance had been set to the desired pressure. By adjusting the rate of flow into the ventricle as measured by the rotameter seen on the upper portion of Fig. 1 the pressure change could be made to occur within a given period (15 sec). Similarly, when the valve was closed ventricular pressure

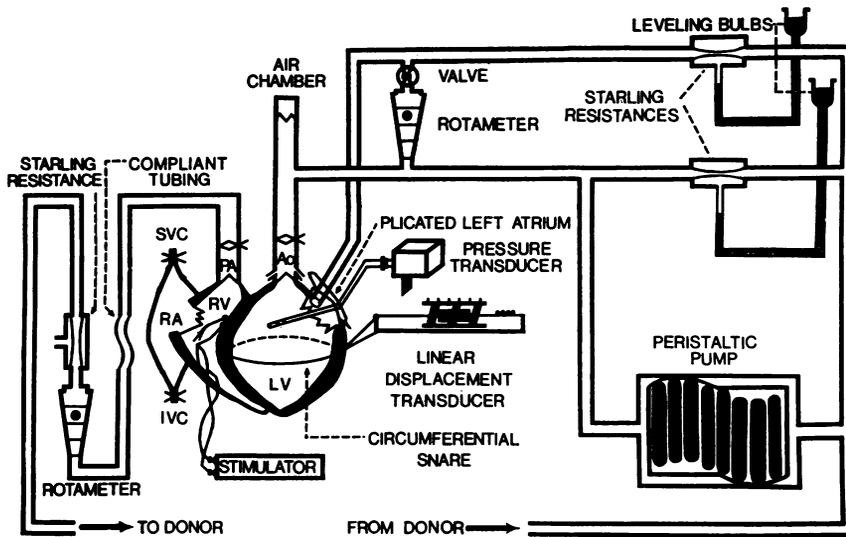


FIGURE 1 Schematic diagram of isolated heart preparation. Arterial blood is pumped from femoral artery of donor to aorta of isolated heart while perfusion pressure is maintained by lower Starling resistance on right. Upper Starling resistance on right regulates ventricular systolic pressure. Coronary sinus blood is returned via pulmonary artery to femoral vein of donor. RA, right atrium; LV, left ventricle; RV, right ventricle; Ao, aorta; PA, pulmonary artery; SVC, superior vena cava; IVC, inferior vena cava.

could be abruptly returned by lowering the pressure applied to the upper Starling resistance seen in Fig. 1. At all times the pressure applied to the lower Starling resistance exceeded that applied to the upper so that the coronary perfusion pressure exceeded or equaled the peak systolic pressure.

The determination of mid-wall radius. Left ventricular mid-wall radius was calculated from the external circumference of the left ventricle at its largest diameter, as measured directly by the snare (Fig. 1). It was assumed that in this plane the ventricle could be treated as a thick-walled sphere (15).

The external radius was calculated as

$$R_e = \frac{C}{2\pi}$$

where: R_e = external radius in centimeters, C = external circumference in centimeters.

The internal radius was calculated as

$$R_i = \frac{\sqrt[3]{(C_d)^3 - (C_e)^3}}{2\pi}$$

where R_i = internal radius in centimeters, C_d = external circumference of the distended ventricle in centimeters, and C_e = external circumference of the ventricle in centimeters after being emptied by suction (15).

The mid-wall radius (R_{mw}) was then calculated as

$$R_{mw} = \frac{R_i + R_e}{2}$$

The determination of relative coronary flow to the inner and outer layers of the left ventricular wall. In 23 experiments relative coronary flow to the inner and outer layers

of the left ventricular wall, including the septum, was determined by the injection of radioactive microspheres into the coronary bed using a previously described technique (18). For this, gamma-emitting Tracer Microspheres (3M Co., St. Paul, Minn.) $15 \mu (\pm 5)$ in diameter were used, labeled either with ^{14}Ce or ^{85}Sr . These were suspended in an aqueous solution of 6% dextran, 0.8% NaCl, and 0.5% Tween 80 (polyoxyethylene sorbitan monooleate). Approximately 60,000–120,000 microspheres were used with each injection which averaged 0.8 ml of the suspension. The activity of each injection was approximately 1.5 μCi .

Before injection the suspension was sonicated to avoid aggregation of the microspheres, and agitated continuously by hand to provide complete dispersion. During these studies coronary perfusion pressure was maintained 5–10 mm Hg higher than the peak left ventricular systolic pressure to insure closure of the aortic valve, and the injection was made rapidly into the root of the aorta.

After the microspheres were injected the hearts were promptly removed from the perfusion apparatus. The atria and right ventricular wall were dissected free and discarded, and the entire left ventricle and septum divided into inner, middle, and outer layers. All sections from the three layers of the ventricle were placed in scintillation vials and counted with a single channel automatic gamma well counting system (Nuclear-Chicago Corporation, Des Plaines, Ill.). The radioactivity of the inner and outer layer caused by both isotopes was determined after correcting for the overlap of their spectral energies, thereby providing a ratio of inner to outer wall coronary flow points in time corresponding to the injection of each isotope.

RESULTS

Demonstration of the Anrep effect under control circumstances. In the preparation used, the systolic pres-

sure of the isovolumically contracting ventricle was controlled as described in methods while the end-diastolic pressure served to indicate its inotropic state. A somewhat more sensitive measurement of the latter was also provided by the circumferential snare which monitored the external diameter of the left ventricle at its equator.

Fig. 2 is a continuous tracing of left ventricular circumference, left ventricular pressure, and left ventricular end-diastolic pressure while the systolic pressure was abruptly elevated from 75 to 150 mm Hg and subsequently returned. During the period shown by the tracing coronary perfusion pressure was maintained constant at 150 mm Hg.

As may be noted from the figure, end-diastolic pressure and ventricular circumference increased with the abrupt increase in systolic pressure. Subsequently, however, there was a gradual decline in both ventricular circumference and end-diastolic pressure after the abrupt increase, while the systolic pressure remained constant, indicating a state of improved contractility which has been termed the Anrep effect (7).

It should also be noted from Fig. 2 that with a parity often found in nature, there was what might be called a "reverse" Anrep effect when the systolic pressure was returned to 75 mm Hg. Both the end-diastolic pressure and the circumference abruptly decreased after the systolic pressure was returned to levels distinctly lower than that noted before the systolic pressure was increased and then gradually approached those control levels. This "reverse" Anrep effect has also been described by others

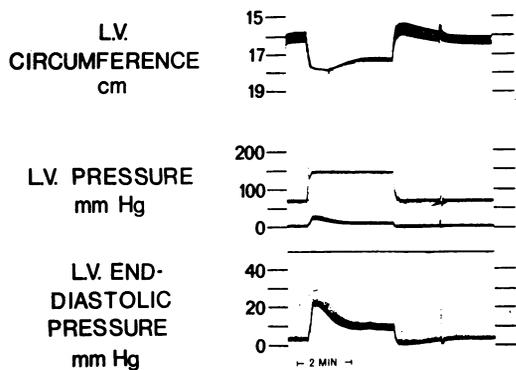


FIGURE 2 Recording of left ventricular circumference, left ventricular pressure (low gain), and left ventricular pressure (high gain) when systolic pressure is abruptly altered while ventricle is contracting isovolumically. Coronary perfusion pressure was maintained at 150 mm Hg. Upper margin of circumference is diastole. Note when systolic pressure is increased from 75 to 150 mm Hg end-diastolic pressure and circumference increase abruptly, but subsequently decrease indicating improved contractility (Anrep effect). Note also when systolic pressure is rapidly decreased from 150 to 75 mm Hg end-diastolic pressure and circumference temporarily fall below control levels. (Reverse Anrep effect.)

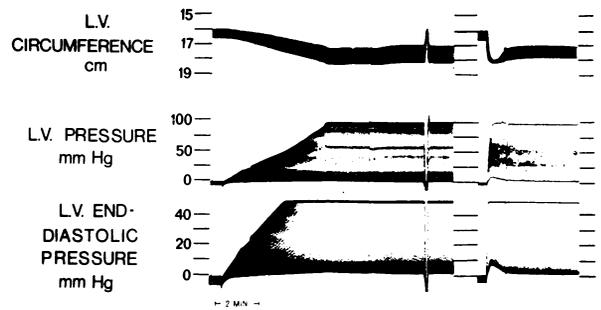


FIGURE 3 Recording of left ventricular circumference, left ventricular pressure (low gain), and left ventricular pressure (high gain) when systolic pressure is slowly increased over a $4\frac{1}{2}$ min period (left panel) and rapidly increased in 15 sec (right panel). Upper margin of circumference is diastole. Note in left panel with slow increase in systolic pressure there was little change in end-diastolic pressure and circumference once the systolic plateau was reached in contrast to right panel where end-diastolic pressure and circumference gradually decreased subsequent to the abrupt increase in systolic pressure (Anrep effect). Note also on left panel absence of demonstrable Anrep effect when systolic pressure is suddenly lowered and returned after ventricle has been contracting isovolumically for several minutes.

(6, 10, 11) but was illustrated here as any hypothetical mechanism of the Anrep effect will have to provide an explanation for the "reverse" effect as well.

At this point, it may be appropriate to emphasize that the extent of the increase in ventricular end-diastolic pressure or circumference that followed an abrupt increase in systolic pressure was, within limits, a direct function of the rate at which the systolic pressure was changed. If, as indicated on the left panel of Fig. 3, the systolic pressure was gradually increased over a $4\frac{1}{2}$ min period there was virtually no change in ventricular circumference or end-diastolic pressure once the systolic plateau had been reached and, therefore, no demonstrable Anrep effect. This is in contrast to a relatively rapid (15 sec) increase in systolic pressure to the same level in the same heart shown on the right panel of Fig. 3, where the Anrep effect is clearly evident.

In addition, Fig. 3 also serves to demonstrate what happens if the systolic pressure is rapidly lowered and immediately returned after the ventricle has been contracting at a constant systolic pressure for several minutes. Under these circumstances, when the systolic pressure is returned there is no discernable Anrep effect, as may be seen from the left panel of the figure.

The influence of altered coronary flow on the Anrep effect. In 62 control experiments the left ventricular systolic pressure of the isolated heart was raised from 5 to 100 mm Hg in 15 sec (± 2). By noting the extent of the decrease in left ventricular end-diastolic pressure and left ventricular mid-wall radius after the systolic plateau had been reached it was possible to provide at

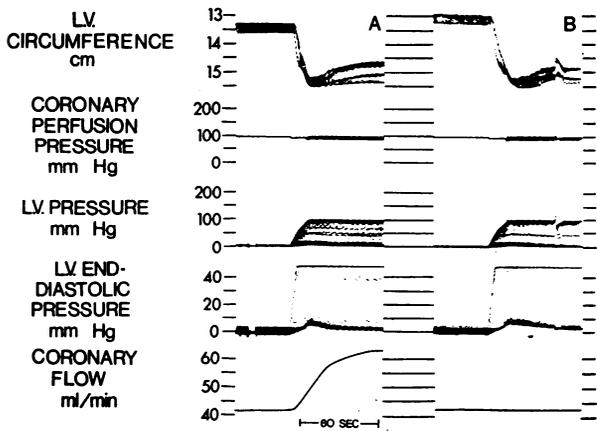


FIGURE 4 Recording of left ventricular circumference, coronary perfusion pressure, left ventricular pressure (low gain), left ventricular pressure (high gain), and coronary flow when left ventricular pressure is raised from 5 to 100 mm Hg in 15 sec under control conditions (panel A) and when coronary flow was maintained constant (panel B). Upper margin of circumference is diastole. Note that decrease in left ventricular end-diastolic pressure and circumference after the systolic plateau has been reached (Anrep effect) still occurs when coronary flow is maintained constant.

least a rough measure of the extent of the Anrep effect under control circumstances.

An example of this may be found in panel A of Fig. 4 and the average results of all 62 control experiments found in Table I. Coronary perfusion pressure was maintained constant at 100 mm Hg during this maneuver. It should be noted from panel A of Fig. 4 that when the systolic pressure was increased there was an attending increase in coronary flow.

In 12 additional experiments, coronary flow was maintained constant during the above described maneuver by compression of the left coronary artery. By manual compression of the artery while carefully monitoring the rotameter shown on the left of Fig. 1, coronary flow could be maintained constant at the level noted before the increase in systolic pressure. As illustrated in panel B of Fig. 4, when coronary flow was maintained constant the decrease in left ventricular end-diastolic pressure and circumference that occurred after the systolic plateau had been reached was comparable to that found in the control experiment (panel A). The Anrep effect, therefore, could not be significantly altered by maintaining coronary flow constant, as has been noted by others (5, 6).

In an additional series of experiments, the same maneuver of increasing the systolic pressure was attempted when coronary flow was increased either by increasing the perfusion pressure or by the administration of various coronary vasodilators such as aminophylline, sodium nitrite, adenosine triphosphate (ATP), or papaverine. The

results of all these studies are included in Table I, and one study in which coronary flow increased by the administration of ATP is illustrated on panel C of Fig. 5.

From this figure two findings should be emphasized. First, with the administration of ATP there was less of an increase in end-diastolic pressure and circumference with the abrupt rise in systolic pressure. Furthermore, once the systolic plateau had been reached, there was little change in end-diastolic pressure and circumference. This virtual abolition of the Anrep effect is in contrast to a control study on the same heart before the infusion of ATP (Fig. 4, panel A) and after the infusion had been discontinued (Fig. 5, panel D).

As may be seen from Table I, the Anrep effect could be significantly reduced by the administration of aminophylline or sodium nitrite in dosages sufficient to cause a moderate increase in coronary flow. It could be further reduced by the increase in coronary flow brought about by an increase in coronary perfusion pressure. With the administration of ATP or papaverine, in dosages which caused maximal or near maximal vasodilation of the coronary bed, the Anrep effect could be abolished. Furthermore, a statistical correlation between the values for coronary flow and percent change in mid-wall radius noted on Table I was highly significant ($P < 0.001$), a

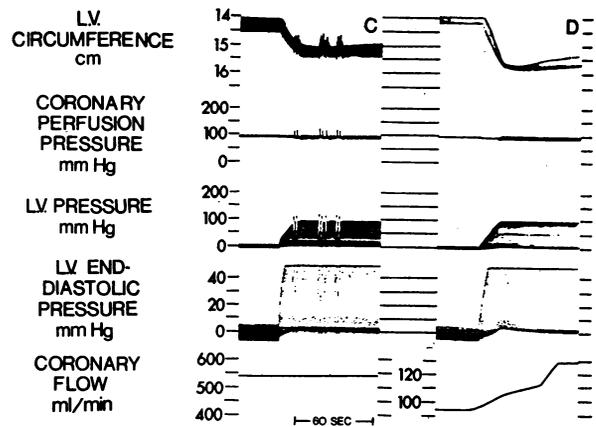


FIGURE 5 Recording of left ventricular circumference, coronary perfusion pressure, left ventricular pressure (low gain), left ventricular pressure (high gain), and coronary flow when left ventricular pressure is raised from 5 to 100 mm Hg in 15 sec, both when coronary bed was near maximally dilated by the infusion of ATP (panel C) and after the infusion had been discontinued (panel D). Upper margin of circumference is diastole. Note with near maximal vasodilation of coronary bed there is less of an increase in end-diastolic pressure and circumference with abrupt rise in systolic pressure and little change after systolic plateau has been reached (abolition of Anrep effect) in contrast to that found after the infusion has been discontinued. Panels A, B, C, and D of Figs. 4 and 5 obtained in consecutive order from the same preparation.

TABLE I
The Effect of Coronary Vasodilation on the Positive Inotropic

Vasodilator	Number of experiments	Average end-diastolic pressure			Significance of difference	Significance of difference from control
		Initial	Final	Difference		
Control	62	10.6	2.9	-7.7	$P < 0.0005$	—
Aminophylline	10	4.3	-0.1	-4.4	$P < 0.0125$	$P < 0.05$
Sodium nitrite	10	4.7	1.7	-3.0	NS	$P < 0.0025$
Increased perfusion pressure	11	3.6	1.9	-1.7	$P < 0.025$	$P < 0.0005$
ATP	17	4.4	3.0	-1.4	NS	$P < 0.0005$
Papaverine	10	-0.1	-0.5	-0.4	NS	$P < 0.0005$

In all hearts the left ventricular systolic pressure was increased from 5 to 100 mm Hg in 15 (± 2) sec as illustrated in Figs. 4 and 5. Initial end-diastolic pressure and mid-wall radius refers to that noted when systolic plateau was reached. Final values, that noted when end-diastolic pressure and mid-wall radius had returned. Coronary flow, that noted after end-diastolic pressure and mid-wall radius had returned. Average rates of

correlation indicating that when coronary flow was greatest the per cent change in mid-wall radius was least.

The effect of increasing coronary flow while the ventricle is contracting at a constant systolic pressure. In a further series of experiments, the effect of increasing coronary flow either by the administration of coronary vasodilators or by increasing coronary perfusion pressure, was noted while the ventricle contracted isovolumically at a constant systolic pressure and heart rate. After a suitable control period, during which ventricular circumference and end-diastolic pressure were observed coronary flow was increased in at least six experiments either by increasing the coronary perfusion pressure or by the administration of sodium nitrite or papaverine. Invariably with the above described intervention there

was a positive inotropic effect manifested both by a decrease in end-diastolic pressure and by a decrease in mid-wall radius. One of these experiments is illustrated in Fig. 6 where there is an attending decrease in left ventricular circumference and left ventricular end-diastolic pressure when coronary flow is increased by increasing the perfusion pressure and a return in end-diastolic pressure and circumference when the perfusion pressure is returned. The results of all of the above described experiments are tabulated in Table II.

Sodium nitrite was specifically selected for this study as it reportedly does not induce a positive inotropic effect when administered to isolated cat papillary muscle preparations (19, 20). Papaverine likewise, if anything, has been shown to depress ventricular contraction in Langendorff perfused frog and turtle hearts (21, 22) which, it may be presumed, are in a state of maximal or near maximal vasodilation. The positive inotropic effect noted in Table II, therefore, is probably not due to any direct action of the drugs on cardiac muscle.

The administration of aminophylline and ATP also was accompanied by a positive inotropic effect. The latter two drugs, however, were not included in Table II as it was suspected that their action might have been due largely to their direct effect on cardiac muscle.

The regional distribution of coronary flow during an abrupt increase in systolic pressure. In 17 consecutive experiments Tracer Microspheres (3M Co., St. Paul, Minn.), 15 μ in diameter labeled with two different radioactive isotopes were infused into the coronary circulation as described in Methods. In each of the 17 hearts microspheres labeled with one isotope were injected while the left ventricle was rapidly filled so as to arrive as the systolic plateau was reached, and microspheres labeled with the other isotope injected later, after the ventricle had been contracting isovolumically for 4 min.

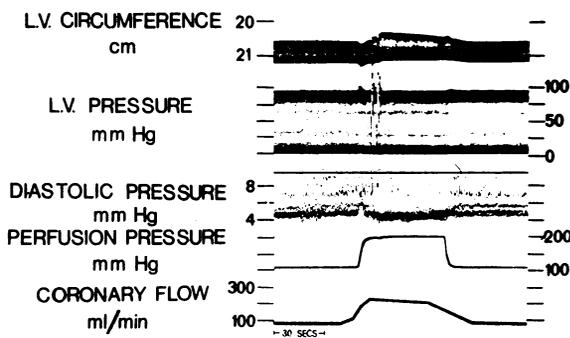


FIGURE 6 Positive inotropic effect of increasing coronary flow by increasing coronary perfusion pressure while left ventricle contracts at a constant systolic pressure and while left ventricular circumference, left ventricular pressure (low gain), left ventricular pressure (high gain), coronary perfusion pressure, and coronary flow are monitored. Upper margin of circumference is diastole. Note decrease in left ventricular circumference and slight decrease in end-diastolic pressure when coronary flow is increased and return to control levels when coronary flow is returned.

Effect that Follows an Abrupt Increase in Systolic Pressure

Average mid-wall radius			Per cent difference	Significance of difference	Significance of difference from control	Average coronary flow	Significance from control
Initial	Final	Difference					
2.37	2.23	-0.14	-5.89	$P < 0.0025$	—	114.0	—
2.20	2.08	-0.12	-5.45	$P < 0.05$	NS	127.9	$P < 0.05$
2.33	2.25	-0.08	-4.27	NS	$P < 0.025$	154.2	$P < 0.0005$
2.14	2.11	-0.03	-1.40	NS	$P < 0.0005$	367.0	$P < 0.0005$
2.15	2.13	-0.02	-0.74	NS	$P < 0.005$	547.7	$P < 0.0005$
1.76	1.75	-0.01	-0.57	NS	$P < 0.005$	447.7	$P < 0.0005$

drug administration as follows: aminophylline, 6 mg/min, sodium nitrite, 25 mg/min, ATP, 10 mg/min, papaverine, 2.5 mg/min. Coronary perfusion pressure was maintained at 100 mm Hg except when increased where indicated from 100 to 180 mm Hg.

The heart was then removed and the left ventricle sectioned into inner, middle, and outer layers. By determining the radioactivity of the inner and outer layers of the ventricular wall the relative coronary flow to the inner and outer layers could be determined both immediately after the abrupt increase in ventricular pressure, when the end-diastolic pressure was highest, and 4 min later, when the end-diastolic pressure had returned to a stable level. In 15 of the 17 hearts there was a decrease in the distribution of coronary blood flow to the inner layers of the ventricular wall immediately after an abrupt increase in ventricular pressure, when the end-diastolic pressure was at its highest, compared to the distribution observed 4 min later.

In these 17 experiments an attempt was made to correlate the per cent change in the ratio of inner to outer wall radioactivity that accompanied the abrupt rise in ventricular pressure with the peak increase in end-dia-

stolic pressure observed. Although correlation between these two variables was without statistical significance ($r = 0.35$) the mean inner to outer wall ratio of radioactivity averaged 1.47 (± 0.09 SEM) immediately after the ventricular pressure was increased compared to 1.72 (± 0.08 SEM) after the ventricle had been contracting isovolumically at a constant pressure for 4 min, a difference that was significant at the $P < 0.025$ level.

In six additional hearts, microspheres labeled by one isotope were injected after the ventricle had been developing a low systolic pressure (5 mm Hg) for a 5 min period and microspheres labeled by the other isotope were injected after the ventricle had been developing 100 mm Hg for a similar length of time. Under these steady-state circumstances no significant difference in the ratio of coronary flow to the inner and outer ventricular layers could be demonstrated. This is consistent with the findings of Domenech et al. (18) who, using a similar tech-

TABLE II
The Positive Inotropic Effect of Coronary Vasodilation while the Left Ventricle is Contracting Isovolumically at a Constant Pressure (100 mm Hg)

Vasodilator	Number of experiments	Average decrease in end-diastolic pressure	Average decrease in mid-wall radius	Per cent decrease in mid-wall radius	Average increase in coronary flow	Per cent increase in coronary flow
Increased perfusion pressure	6	mm Hg 1.08	cm 0.05	1.97	ml 62.6	95.8
Sodium nitrite	6	1.02	0.05	2.32	54.1	100.0
Papaverine	9	5.03	0.21	9.83	232.4	350.8

In all experiments a positive inotropic effect was indicated by a decrease in both end-diastolic pressure and mid-wall radius when coronary flow was increased by increasing perfusion pressure from 100 to 180 mm Hg or by administration of either sodium nitrite (25 mg/min) or papaverine (2.5 mg/min).

nique, could demonstrate no significant difference in the ratio of radioactivity of inner and outer layers of the working ventricle when compared with the nonworking ventricle.

The intracardiac electrocardiogram during an abrupt increase in ventricular pressure. In the preceding sections, data have been presented consistent with the hypothesis that ischemia of the subendocardial ventricular layers accompanies an abrupt increase in the pressure developed by the ventricle. Accordingly, an attempt was made to obtain electrocardiographic evidence of this from a bipolar electrode within the ventricular cavity. An example of this is illustrated by Fig. 7 which is a continuous tracing of left ventricular circumference, the intraventricular electrocardiogram, left ventricular end-diastolic pressure, and left ventricular pressure during an abrupt increase in ventricular pressure and also during and after partial occlusion of the left coronary artery. Here it may be seen from the high speed tracings, A, B, and C of Fig. 7, that with an abrupt increase in ventricular pressure there is first a lowering of the T wave (A) followed by an inversion of the T wave and a depression of the S-T segment (B) when compared with the S-T and T wave pattern seen after the ventricle has been developing a constant pressure for over 4 min (C). When the left coronary artery was partially occluded (the period indicated by the bar between C and D) there was an increase in left ventricular end-diastolic pres-

sure and circumference to levels similar to that noted immediately after the abrupt increase in ventricular pressure. Again there was a depression of the T wave (D) followed by T wave inversion and depression of the S-T segment (E) before the normal pattern was regained (F). It should be emphasized that the illustrated tracings were obtained from electrodes situated within the ventricular cavity. No significant changes were found in the external electrocardiogram when the ventricular pressure was abruptly increased.

Fig. 8, in contrast to the previous figure, shows tracings of the intracardiac electrocardiogram obtained when the intraventricular pressure is abruptly increased during papaverine administration and consequent dilation of the coronary bed. Under these circumstances the S-T and T wave patterns observed immediately after the abrupt increase in ventricular pressure are similar to that found after the ventricle has been developing a constant pressure for several minutes, and do not reflect ischemia.

DISCUSSION

As stated in the introduction, the object of this report is to present evidence supporting the hypothesis that the Anrep effect is primarily the recovery from a negative inotropic effect which accompanies an abrupt increase in the pressure developed by the ventricle, and that this negative inotropic effect is caused by subendo-

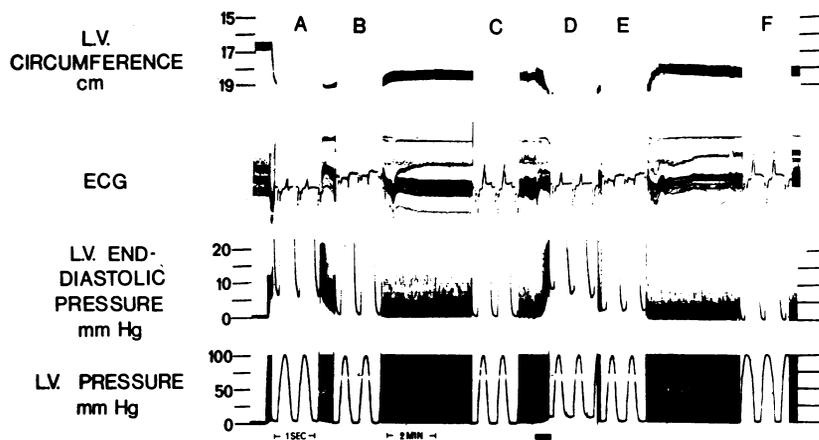


FIGURE 7 Recording of left ventricular circumference, intracardiac electrocardiogram, left ventricular pressure (high gain), and left ventricular pressure (low gain) after an abrupt increase in ventricular pressure and during and after partial occlusion of the left coronary artery. Upper margin of circumference is diastole. Rapid tracings of ventricular circumference were not obtained. Note on ECG tracing, depression of T wave (A) and inversion of T wave as well as depression of S-T segment (B) immediately after abrupt increase in ventricular pressure in contrast with that found after ventricle had been developing a constant pressure for over 4 min (C). Note also with partial occlusion of left coronary artery (bar) there is also transient lowering of T wave (D) as well as T wave inversion and depression of S-T segment (E) in comparison with tracing obtained after recovery (F).

cardial ischemia which, in turn, is corrected by vascular autoregulation of the coronary bed.

Normally, there is equal distribution of coronary flow to the inner and outer layers of the ventricular wall as has been demonstrated by others (18). With an abrupt increase in systolic pressure there is temporary ischemia of the inner portion of the ventricular wall, presumably due to the high intramural pressure within this area (23, 24). Due to this ischemia myocardial contractility is reduced, as manifested by a high rise in end-diastolic pressure and volume. By vascular autoregulation of the coronary bed, this condition is slowly corrected with a redistribution of coronary flow and a consequent improvement in contractility which has been termed the Anrep effect (7). It is important to emphasize that this redistribution can occur, albeit to a somewhat lesser extent, when total coronary flow is maintained constant (5, 6).

There are a number of arguments which support the "recovery" hypothesis as an explanation of the Anrep effect. First, the Anrep effect is not seen in papillary muscle preparations (8, 11). Here, one might argue, that the Anrep effect is an intrinsic form of autoregulation and that papillary muscles are too poorly oxygenated to show it. However, it must be remembered that papillary muscles are quite capable of showing the Bowditch effect, an accepted autoregulatory process seen both in papillary muscle preparations and in intact hearts (8).

It would not seem unreasonable, therefore, to postulate that the Anrep effect is not seen in papillary muscle preparations because they are devoid of coronary flow and do not have the unique geometry of the ventricle. With such a geometry, one might expect large abrupt changes in ventricular pressure to produce large abrupt changes in intramural pressure, particularly in the subendocardial layers (23, 24), making it necessary for the ventricle to rely heavily on the compensatory mechanism of vascular autoregulation to avoid ischemia, a mechanism that requires time.

Second, as a corollary to this, with slow changes in systolic pressure the compensating mechanism of autoregulation is adequate as indicated on the left panel of Fig. 3 where with a slow increase in systolic pressure there is no acute rise in end-diastolic pressure and circumference and hence no appreciable compensatory Anrep effect. This is in contrast to the right panel of Fig. 3, where a relatively abrupt rise in the systolic pressure of the same ventricle is accompanied by relatively greater increases in end-diastolic volume and circumference which are, in turn, compensated for by the Anrep effect. Furthermore, with an abrupt lowering and immediate return of systolic pressure (left panel, Fig. 3) after the ventricle has developed a constant

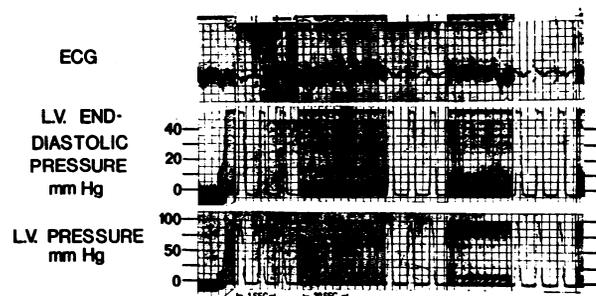


FIGURE 8 Recording of intraventricular electrocardiogram, left ventricular pressure (high gain), and left ventricular pressure (low gain) after an abrupt increase in ventricular pressure when coronary bed is near maximally dilated by administration of papaverine (4.6 mg/min). Note virtually no change in S-T segment and T wave pattern (in contrast with Fig. 8) as well as minimal change in end-diastolic pressure after systolic plateau is reached.

pressure for several minutes, no Anrep effect is noted. Here, it may be presumed, that the vascular autoregulatory forces tending to insure adequate circulation to the subendocardial layers of the ventricle had insufficient time to relax.

Third, with the administration of potent coronary vasodilators, such as papaverine or ATP, adequate circulation to the subendocardial layers of the ventricular wall could be assured during the period when the systolic pressure abruptly increased. Here, there is no subendocardial ischemia and consequently no corrective Anrep effect (Fig. 5). Moderately effective coronary vasodilation was also achieved with other drugs as well as by increasing the perfusion pressure. Under these circumstances, it is important to emphasize that the ability of a vasodilator to reduce the Anrep effect was in direct proportion to its ability to increase coronary flow.

Fourth, from the experiments in which the regional distribution of coronary flow was determined by using radioactive microspheres, the ratio of inner to outer left ventricular wall coronary flow was significantly reduced immediately after an acute rise in left ventricular systolic pressure, when compared with the ratio noted after the ventricle had been developing a constant systolic pressure for several minutes.

Fifth, the intraventricular electrocardiogram provided evidence of subendocardial ischemia by S-T segment and T wave changes immediately after an acute increase in left ventricular systolic pressure (Fig. 7). These changes were similar to those noted in the same preparation when ischemia was produced by coronary constriction. Furthermore, no such changes were noted when coronary vasodilators were administered and the systolic pressure abruptly increased (Fig. 8).

The question naturally arises as to how the above described hypothesis can explain the "reverse" Anrep

effect illustrated by Fig. 2, and also observed by others (6, 10, 11). From the figure, it should be noted that when systolic pressure was increased from 75 to 150 mm Hg, maintained there for over 3 min, and abruptly decreased back to 75 mm Hg, end-diastolic pressure and circumference fell to levels below control, then gradually returned. This again is consistent with the hypothesis, as with an abrupt decrease in the systolic pressure of the ventricle the vascular autoregulatory forces tending to protect against ischemia of the inner ventricular wall would temporarily remain effective and one would naturally expect a period of excessive coronary flow to the inner ventricular layers. It is presumed that this excess flow, in itself, is capable of causing a positive inotropic effect.

While the last statement may not be generally accepted, recent evidence has appeared to support it (20, 25). Furthermore, if coronary flow was sufficiently increased in the isolated heart preparation, while the ventricle was developing a constant systolic pressure, a positive inotropic effect was manifested by a decrease in both end-diastolic pressure and circumference (Fig. 6, Table II). This appeared whether or not coronary flow was increased either by increasing the perfusion pressure or by the administration of coronary vasodilators that were shown not to have a direct inotropic effect on cardiac muscle (19–22). Even the hyperemia induced by a brief period of coronary occlusion was noted to be accompanied by a positive inotropic effect (Fig. 7).

Alternatively one could speculate that substances presumably involved in the autoregulatory mechanism such as adenosine (26) could have a direct positive inotropic action on cardiac muscle. Until this is firmly established the authors would prefer the previously offered explanation which is more easily reconciled with the observation that if coronary flow is increased by increasing perfusion pressure there is an attending positive inotropic effect.

The presented hypothesis is, incidentally, consistent with various additional characteristics of the Anrep effect noted earlier. The magnitude of the effect has been shown to be proportional to the magnitude of the abrupt change in pressure (9). Furthermore, the effect is greater at faster heart rates (9). At higher systolic pressures and faster heart rates one would expect the metabolic needs of the ventricle to be greater, and therefore the effect of ischemia and its subsequent correction to be more pronounced. Likewise, in the same publication it was noted that the effect was diminished in hearts blocked with β -adrenergic blocking agents, an observation which led the authors to the conclusion that catecholamines might be involved in the mechanism of the Anrep effect. The authors would now prefer

to attribute the finding of a diminished effect in beta-blocked hearts to the diminished metabolic needs of these ventricles. In a previous report a loss of myocardial potassium was noted to follow the Anrep effect (10). Although the loss appeared somewhat later than the effect in the referred report, potassium loss is an established sequela of myocardial ischemia (27).

Should the presented hypothesis stand the test of time, its implications deserve brief mention. First, it would serve to warn the investigator that a period of instability follows an abrupt change in the pressure developed by the ventricle and that the contractility of the ventricle immediately after such a change may not be indicative of its full capacity. Second, as vasodilation of the coronary bed is accompanied by a positive inotropic effect, it may be presumed that normally, a certain number of myofibrils, particularly in the subendocardial layers of the ventricle, are exerting less than their full capabilities because of ischemia. Furthermore, the positive inotropic action of agents that are coronary vasodilators may be in part due to their direct action on cardiac muscle and in part due to their action on the coronary vasculature. The clinical implications here are obvious, to the extent that one can extrapolate to the intact animal.

Third, again to the extent that one can extrapolate, the hypothesis should provide the clinician with the warning that the ventricle may be in a temporary state of jeopardy after an abrupt rise in systolic pressure due to the attending subendocardial ischemia as well as its subsequent correction. In the studies described in this report arrhythmias frequently accompanied and immediately followed the abrupt increases in systolic pressure. Here it is important to note that ventricular fibrillation more frequently follows the relief of coronary occlusion than it follows the occlusion itself (28). To this extent, a precise mechanism is provided to explain arrhythmias and often death in untrained individuals performing moderate physical exertion, and who are disposed towards radical increases in blood pressure with sudden exercise. Furthermore, by observing ventricular end-diastolic pressure or the intracardiac electrocardiogram after an abrupt rise in systolic pressure one might be provided with a measure of the adequacy of the subendocardial circulation in patients suspected of myocardial ischemia.

Finally, it is hoped that the hypothesis presented here might serve to clarify an awkward discrepancy between the performance of cardiac muscle strip preparations and that of the intact heart as well as to provide insight into an aspect of ventricular behavior that has remained obscure for some time. At this point, it might be appropriate to repeat the explanation for the Anrep effect proposed by Patterson, Piper, and Starling over

half a century ago (3): "But at the higher pressure there is a marked increase in the blood supply to the heart muscle. The improved nourishment of the muscle causes an improvement in its physiological condition, and this improvement shows itself by an increase of the tension set up at each degree of contraction in the muscle fiber and therefore a diminution in the length of the muscle fiber necessary to produce a certain tension. We therefore find that the primary dilatation of the heart is followed by a slow recovery, as shown by a diminution of its mean volume."

The authors take note that the data submitted in the present report are largely consistent with the position taken by Patterson et al. in 1914.

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REFERENCES

- Knowlton, F. P., and E. H. Starling. 1912. The influence of variations in temperature and blood-pressure on the performance of the isolated mammalian heart. *J. Physiol. (Lond.)* **44**: 206.
- von Anrep, G. 1912. On the part played by the supra-renals in the normal vascular reactions of the body. *J. Physiol. (Lond.)* **45**: 307.
- Patterson, S. W., H. Piper, and E. H. Starling. 1914. The regulation of the heart beat. *J. Physiol. (Lond.)* **48**: 465.
- Starling, E. H. 1918. The Linacre Lecture on the law of the heart (1915). Longmans Green & Co. Ltd., London.
- Rosenblueth, A., J. Alanís, E. López, and R. Rubio. 1959. The adaptation of ventricular muscle to different circulatory conditions. *Arch. Int. Physiol. Biochem.* **67**: 358.
- Sarnoff, S. J., J. H. Mitchell, J. P. Gilmore, and J. P. Remensnyder. 1960. Homeometric autoregulation in the heart. *Circ. Res.* **8**: 1077.
- Sarnoff, S. J., and J. H. Mitchell. 1961. The regulation of the performance of the heart. *Am. J. Med.* **30**: 747.
- Blinks, J. R., and J. Koch-Weser. 1963. Physical factors in the analysis of the actions of drugs on myocardial contractility. *Pharmacol. Rev.* **15**: 531.
- Monroe, R. G., C. G. La Farge, W. J. Gamble, A. Rosenthal, and S. Honda. 1968. Left ventricular pressure-volume relations and performance as affected by sudden increases in developed pressure. *Circ. Res.* **22**: 333.
- Sarnoff, S. J., J. P. Gilmore, J. H. Mitchell, and J. P. Remensnyder. 1963. Potassium changes in the heart during homeometric autoregulation and acetyl strophanthidin. *Am. J. Med.* **34**: 440.
- Gilmore, J. P., H. E. Cingolani, R. R. Taylor, and R. H. McDonald, Jr. 1966. Physical factors and cardiac adaptation. *Am. J. Physiol.* **211**: 1219.
- Monroe, R. G., C. G. La Farge, W. J. Gamble, R. P. Hammond, and C. L. Morgan. 1966. Norepinephrine release and left ventricular pressure in the isolated heart. *Circ. Res.* **19**: 774.
- LaFarge, C. G., R. G. Monroe, W. J. Gamble, A. Rosenthal, and R. P. Hammond. 1970. Left ventricular pressure and norepinephrine efflux from the innervated heart. *Am. J. Physiol.* **219**: 519.
- Levy, M. N., E. S. Imperial, and H. Zieske, Jr. 1963. Ventricular response to increased outflow resistance in absence of elevated intraventricular end-diastolic pressure. *Circ. Res.* **12**: 107.
- Monroe, R. G., W. J. Gamble, C. G. LaFarge, A. E. Kumar, and F. J. Manasek. 1970. Left ventricular performance at high end-diastolic pressures in isolated, perfused dog hearts. *Circ. Res.* **26**: 85.
- Monroe, R. G., C. G. LaFarge, W. J. Gamble, A. E. Kumar, and F. J. Manasek. 1971. Left ventricular performance and coronary flow after coronary embolization with plastic microspheres. *J. Clin. Invest.* **50**: 1656.
- Gregg, D. E. 1950. Coronary circulation in health and disease. Lea & Febiger, Philadelphia.
- Domenech, R. J., J. I. E. Hoffman, M. I. M. Noble, K. B. Saunders, J. R. Henson, and S. Subijanto. 1969. Total and regional coronary blood flow measured by radioactive microspheres in conscious and anesthetized dogs. *Circ. Res.* **25**: 581.
- Zellis, R., D. T. Mason, J. F. Spann, and E. A. Amsterdam. 1970. The mechanism of action of nitroglycerin in the relief of angina pectoris: reduction of myocardial oxygen requirements by extracoronary vasodilation and its attenuation by the chronic administration of isosorbide dinitrate. *Ann. Intern. Med.* **72**: 779. (Abstr.)
- Abel, R. M., and R. L. Reis. 1971. Effects of coronary blood flow and perfusion pressure on left ventricular contractility in dogs. *Circ. Res.* **27**: 961.
- Hanzlik, P. J. 1921. Comparative effect of morphine and alkaloids of the bengyloquinolin group on cardiac muscle. *J. Pharmacol. Exp. Ther.* **17**: 445.
- Macht, D. L. 1961. A pharmacologic and clinical study of papavarine. *Arch. Intern. Med.* **17**: 786.
- Kirk, E. S., and C. R. Honig. 1964. An experimental and theoretical analysis of myocardial tissue pressure. *Am. J. Physiol.* **207**: 361.
- Armour, J. A., and W. C. Randall. 1971. Canine left ventricular intramyocardial pressures. *Am. J. Physiol.* **220**: 1833.
- Bacaner, M. B., F. Lioy, and M. B. Visscher. 1971. Coronary blood flow, oxygen delivery rate and cardiac performance. *J. Physiol.* **216**: 111.
- Rubio, R., and R. M. Berne. 1969. Release of adenosine by the normal myocardium in dogs and its relationship to the regulation of coronary resistance. *Circ. Res.* **25**: 407.
- Case, R. B., M. G. Nasser, and R. S. Crampton. 1969. Biochemical aspects of early myocardial ischemia. *Am. J. Cardiol.* **24**: 766.
- Stephenson, S. E., Jr., R. K. Cole, T. F. Parrish, F. M. Bauer, Jr., I. T. Johnson, Jr., M. Kochtitzky, J. S. Anderson, Jr., L. L. Hibbitt, J. E. McCarthy, E. R. Young, J. R. Wilson, H. N. Meiers, C. K. Meador, C. O. T. Ball, and G. R. Meneely. 1960. Ventricular fibrillation during and after coronary artery occlusion. Incidence and protection afforded by various drugs. *Am. J. Cardiol.* **5**: 77.