Effects of Epinephrine on Frog Ventricle

By Richard A. Henney, Ph.D.

The possible methods by which epinephrine may increase cardiac output, though in practice they are not completely independent, can be separated for purposes of discussion as follows: (1) increase in end-diastolic volume; (2) decrease in end-systolic volume; and (3) increase in heart rate.

The first 2 factors determine the stroke volume. Assuming a constant heart rate, the end-diastolic volume can be increased by only one of the following factors: (1) an increase in diastolic time by shortening systole; (2) decrease in the average resistance to filling (retenience) either by decreasing the average resistance of the myocardium during diastole (an increase in distensibility) or by hastening relaxation after contraction, or both; and (3) by increasing the filling pressure.

A decrease in the end-systolic volume (assuming constant end-diastolic volume) can be accomplished by an increase in the strength of contraction, an increase in its duration, or by any combination of these.

It is well known that epinephrine increases the strength of contraction and the heart rate. However, little conclusive evidence has been presented about the effects of epinephrine on relaxation and resistance to filling. The present series of experiments were performed in order to determine these effects.

Methods

The methods were similar to those used in the preceding experiment; however, some changes were made. Instead of a recording pipette, a "U" tube with a 16 gage needle attached was used to connect the heart chamber to a beaker, and the pressure drop between the heart container and beaker was used to measure the flow rate.

The extracardiac pressures (within heart container) and the lateral isotonic pressures were recorded by means of 2 Statham gages (F and G) and a Hathaway recorder with a paper speed of either 4 or 10 inches per second (fig. 1). In some experiments, valves (J and K) were introduced in both the inflow and outflow channel, which permitted an additional resistance (hypodermic needle) to be inserted on the outflow side. Isochoreic (isovolumetric) pressures were often recorded.

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\( P_e \) dropped below the base line (fig. 2), the heart was actively expelling its contents back into the reservoir. Pressures above the base line indicated filling. Since the filling pressure is constant, the rate of change of the transmural pressure is indicative of the relaxation rate, and is calculated from the pressure-time curve from manometer F (fig. 1). Whereas this is usually approximated as the difference between the pressure recorded by an intracardiac transducer, transmural ventricular pressures, and flow rates were calculated from the information obtained from the manometers and the resistance of the inflow cannula and "U" tube. 

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Figure 1

planimeter, since during diastole the area of the P0-time curve is proportional to the total flow. Another measurement of relaxation is the time required from the beginning of filling until the plateau is reached (fig. 2 A-B, relaxation time) at which time the resistance is at a minimum and inflow rate becomes constant.

Results
Without Valves or Added Resistors
Effect of Pressure Changes on the Relaxation Rate
Normal ventricle. Within a range of small filling pressures (1 to 2 cm.) the rate of relaxation is constant, and therefore independent of the pressure. However, with higher filling pressures gradually applied, the rate of relaxation becomes proportional to the pressure. Previous experiments have established that sudden pressure increases lead to increases in the minimum resistance.1 However, the first effect of a pressure increase is an acceleration in the rate of relaxation, followed by a decrease if high (> 8 cm. H2O) pressures are used. If the pressure is then reduced, the rate of relaxation continues to be slower than that previously observed for the lower pressure, but the relaxation rate returns to normal over a period of 5 to 10 minutes.

Hypodynamic ventricle. In a ventricle with a small stroke volume, the relaxation rate is small, and initially proportional to the filling pressure. With higher pressures, the relaxation rate increases, but still remains relatively small if the ventricle does not respond to increased filling pressure by an increased ejection (hypodynamic heart). This may be related to the low pH and hypoxia which accompany small stroke volumes in this preparation.

Effect of Frequency on the Rate of Relaxation
If the filling pressure is low or medium (1 to 8 Gm.), the rate of relaxation is slowed by both fast and slow contraction rates, and has
a particular rate at which the most rapid relaxation occurs. Thus, with about 5 cm. of filling pressure, the maximum relaxation rate is observed at about 15 to 20 contractions a minute. In contrast to low pressures, in 1 experiment in which the filling pressure was 15 cm., the slowest relaxation rate occurred when the contraction rate was 30 beats/min. Higher or lower rates of contraction resulted in a great increase in the relaxation rate.

Effects of Epinephrine on the Relaxation Rate and Diastolic Relaxation Time

Low pressures (1 to 2 cm.) and a contraction rate of 12 beats/min. At low pressures, the normal relaxation is sometimes greatly slowed, even without epinephrine. In hearts with a fairly rapid relaxation at low pressures, epinephrine greatly lengthens the diastolic relaxation time and greatly reduces the maximum relaxation rate (fig. 3). However, if sufficient time is given for complete filling by adjusting the contraction rate, the volume intake during diastole will usually be slightly increased, in spite of the slowing of relaxation. This indicates probably a decrease in the end systolic volume as a result of the inotropic effect of epinephrine.

At 5 cm. filling head, contraction rate 12 to 30 beats/min. In 9 out of 13 cases, the maximum rate of relaxation was slower with epinephrine. In 2 instances, the maximum rate remained the same. In only 2 experiments did the rate increase. In one of these experiments, the stroke volume was small. In the other, the beginning of the relaxation was considerably slower. In all but 2 cases, the relaxation time (time from the beginning of filling to the plateau) increased.

At pressures from 8 to 15 cm. and contraction rate from 12 to 30 beats/min. With the filling pressure at 8 cm., 3 out of 4 experiments showed an increase in the maximum rate of relaxation, while 1 experiment showed no change. With new preparations, 2 out of 4 at 10 to 15 cm. of filling pressure showed no change, while the other 2 showed a decrease in maximum rate of relaxation. However, in all experiments the diastolic relaxation time was increased after using epinephrine. At continuous filling pressures of 10 cm. or greater, the heart appeared distended and gradually contracted less effectively, which was irreversible upon reducing the pressure. It is presumed that these hearts were damaged by the high pressure.

Effects of Epinephrine on the Minimum Renitenee

In table 1 are the values of the minimum renitenee (P/Flow) of the heart at 20 to 22°C, before and after the addition of 0.2 µg of epinephrine per ml. (Winthrop Laboratories). The last 2 columns in the table show that there is no consistent change in this value due to epinephrine, though the dosage consistently increased systolic pressure. In hearts that are hypodynamic either naturally or from the effects of sodium pentobarbital, epinephrine does lower the Rm toward the normal value.1

Effect of Valves and Added Outflow Resistance on the Relaxation Rate

With the insertion of valves, it is possible to have a low filling pressure, and yet insert resistance into the outflow channel. The addition of a resistor (no. 18 needle attached to reservoir return tube) to the system only slightly affected the rate of relaxation of the normal heart. In some cases, the relaxation rate continuously decreased, because of probably a reduction of stroke volume and the effects of hypoxia. With epinephrine and valves but no resistor the rate of relaxation was greatly slowed, as in the case of those
Table 1

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<th>Experiment no.</th>
<th>Heart rate Cont./min.</th>
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<th>Relaxation time (sec.)</th>
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*Filling pressure 5 em.; no valves.

Experiments without valves. With the addition of the resistor, however, the rate of relaxation usually approached the normal rate (before administering epinephrine and inserting resistance), and in some cases was more rapid.

**Effect of Epinephrine on Isochoric and Isobaric Contractions**

Epinephrine increases the maximum rate of relaxation in isochoric contractions. However, contraction time (period of positive tension greater than the filling head) appears to remain constant, although Segall and Anrep reported a lengthening of contraction time with epinephrine. 8

In comparing isobaric to isochoric contractions, it can be seen (fig. 2) that the maximum rate of volume change (isobaric) occurs before the maximum tension (isochoric), and after administering epinephrine, this difference becomes even more pronounced so that the isobaric volume change is completed considerably earlier than the corresponding contraction time of the isochoric heart.

**Discussion**

Several investigators 4-6 have stated that epinephrine has a direct effect on cardiac muscle during diastole. Lundin 7 and F. Moore (personal communication) have shown that the resistive properties to stretch, and thus, stiffness and viscosity, are not changed in frog ventricular tissue by the addition of adrenaline or epinephrine, respectively. The present experiments on the intact frog ventricle substantiate these conclusions.

In comparing the maximum rate of relaxation of the isochoric contraction in the normal and epinephrine-treated heart, it is obvious that the rate of relaxation is increased to a greater extent than the pressure is increased after epinephrine. Therefore, it seems probable that epinephrine increases the relaxation rate independently of its inotropic effect in increasing pressure.

Epinephrine may influence the relaxation in the isochoric contraction by prolonging the contraction time of some elements in a similar fashion to that observed by Goffart and Ritchie with skeletal muscle. 8 However, none of the elements must be prolonged beyond the maximum time of the elements of the normal heart, or else the total positive tension time would be prolonged. If certain elements were prolonged, while others are unchanged, subsequent relaxation would apparently be rapid as more elements would relax together.
The slowing of relaxation during diastole with epinephrine in isobaric contractions may seem at first to be contradictory to the above conclusions. Lundin, however, has shown that a cardiac fiber in the contracted state can lose its tension when released, but when subsequently stretched, develops a greater tension at a given length than the isometric tension at that length. Thus, a heart contracting with much force can reach a sufficiently small volume so that most of the tension disappears, and filling can then commence before the diastolic state is fully established. Outflow would then lead to a re-establishment of some tension, due to the stretching of fibers. Also, since epinephrine increases the amount of tension per unit stretch of contracted fibers, this would further increase the resistance to filling so long as there is any residual tension from the preceding systole. By these means, filling would be slowed and controlled by the relaxation rate. In fact, pressure changes have little effect on the initial relaxation rate after epinephrine, (fig. 3) or at very low pressures. At a large volume, however, the linear stretch of a heart during filling may be too slow to produce tension if relaxation is also occurring. For a given flow rate, the rate of linear stretch would be inversely proportional to the square of the heart's radius (assuming the heart to be spherical). Epinephrine, by accelerating the relaxation rate of contractile units, would then accelerate the relaxation rate during filling. A resistance in the outflow channel would serve to increase the end systolic volume, and thus, enhance relaxation.

Increasing the filling pressure, in the preparation without valves, however, would act in 2 opposite directions, since not only will the outflow resistance increase, but also the inflow rate. This is probably the reason for the conflicting results using high filling pressures without valves.

The contraction time is decreased with increasing contraction rates. This would be expected to accelerate the relaxation rate. By this means, a heart with a small end-systolic volume may fill rapidly, even with epinephrine. At low contraction rates, however, the treppe effect will produce weak contractions which would have 2 effects on increasing the relaxation rate: (1) increasing the size of the heart at the beginning of filling, and (2) prolonging the ejection time so that filling only occurs after the residual tension from the preceding systole is over. There are, therefore, both high and low rates of contraction that will produce rapid relaxation at least with some filling pressures.

Summary

Thirty-six isolated frog ventricles were attached to an inflow cannula with stopcocks that could permit direct systolic ejection back into the reservoir, return flow back to the reservoir by another route through a valve, or isochoric contractions. The heart, enclosed in a container with a "U" tube outlet, produced pressure changes (extra-cardiac) which could be used in determining the in-flow rate and transmural pressures. The rate of change of the transmural pressure was calculated for the frog ventricle during early diastole. This value was taken as a measurement of the rate of relaxation. The effects of epinephrine (.02 mg./ml.) were studied. At low filling pressures without valves (and therefore with outflow pressure equal to inflow pressure), epinephrine slows the rate of relaxation, although other inotropic effects, such as an increase in stroke volumes, are present. If, however, the heart contracts against a high outflow pressure or resistance the rate of relaxation is increased by epinephrine. The slowing of relaxation in the former case is a result of filling commencing before relaxation is complete. In the isochoric heart, epinephrine does not change the time of positive tension, but does accelerate the relaxation after contraction.

Summario in Interlingua

Trenta-seis isolite ventriculos de rana essaeva attache a un cannula de influxo con obturatores que permitteste lo directo retro-ejection systolic a in le reservoir, lo refluxo al reservoir per un altec circuito via un valvula, o contractiones isochoric. Le corde, inclusite in un receptacle con un efflux a tube in "U," produciva alteraciones de pression (extra-cardiac) que poteva esser usate in determinar le intensi-
tate del influxo e le pressiones transmural. Le magnitude delle alteration in le pressione transmural esseva calculated pro le ventriculo del rana durante le coeliasasto. Iste valor esseva acceptede como measure del magnitude del relaxation. Le effetto de epinephrina (0,02 μg/ml) esseva studiate. A basse pressiones de replenamento sin valvulas (e assi sin pression de effluxo equal al pression de influxo), epinephrina re-lenta le progresso del relaxation, ben que altere effectos isotropic—como per exemplo un augmento del voluminos per pulso—es presente. Tamen, si le corde se contrale contra un alto pression e resistencia de effluxo, le relaxation es promovite per epinephrina. Le relenteamento del relaxation in le prime de iste casos es le resultato del facto que le replenamento commeccia ante que le relaxation es complete. In le corde isochoric, epinephrina non altera le tempore de tension positivo sed accelerat le relaxation post contraction.

References


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