Experimental Myocardial Ischemia

Dynamic Alterations in Ventricular Contractility and Relaxation with Dissociation of Speed and Force in the Isovolumic Dog Heart

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SUMMARY Although the time course of changes in myocardial function during ischemia has been demonstrated for the papillary muscle, this time course in the intact heart is less well understood. Accordingly, in 24 isolated, isovolumic, perfused dog hearts, coronary perfusion pressure (PP) was lowered to various fixed levels. Left ventricular developed pressure (LVP) rapidly fell and reached 63 ± 3% of control at 1 minute of ischemia and 50 ± 5% at 6 minutes; this was due primarily to an abbreviation of time to peak tension (TP). dP/dt was 70 ± 3% of control at 1 minute and 56 ± 5% at 6 minutes. The rate of relaxation as reflected by negative dP/dt declined as well to 49 ± 4% of control at 1 minute of ischemia and to 41 ± 4% of control at 6 minutes. These changes were directly correlated with the decrease in PP. When PP was restored to normal, an overshoot of LVP and dP/dt was noted, peaking at 1 minute, returning to control by 5 minutes, and then gradually declining to 90 ± 2% of control following 25 minutes of recovery. Depression of the rate of relaxation was reduced, but persisted throughout recovery. Diminution of force development early in ischemia is due primarily to decreased duration of contraction accompanied by a decrease in relaxation rate. Later, the rate of force development also falls, but some preservation of force development may result from the return toward normal of the duration of contraction.

THE INFLUENCE of acute ischemia on the function of the heart has been a subject of extensive investigation. Although contractile force declines rapidly during acute ischemia, the precise mechanisms by which this occurs are still unclear. The time course of changes in myocardial function during hypoxia has been studied for the isolated cat papillary muscle, and changes in force, velocity, and duration of contractions have been shown to be altered. However, the change in each of these variables relative to time appears to be different. In the present study several parameters of myocardial function have been studied in the isolated isovolumic canine heart in which coronary perfusion pressure could be altered quickly and maintained at various fixed levels. The differential effects of ischemia on the rate of pressure development, developed pressure, duration of contraction, and ventricular relaxation have been explored during periods of reduced coronary perfusion pressure and during subsequent recovery.

Methods

An isolated, isovolumic, canine heart perfused with blood from a second dog (Fig. 1) was prepared; 24 mongrel dogs of both sexes which averaged 20 kg in body weight were used. After the induction of anesthesia with intravenous sodium pentobarbital (30 mg/kg), artificial ventilation was instituted with a positive-pressure, fixed-volume pump. The thorax was opened widely, and anticoagulation was produced with 10,000 U of sodium heparin. A polyethylene (PE) cannula was placed in the innominate artery and connected to a reservoir filled with blood through cannulas placed in both femoral arteries of the second anesthetized, anticoagulated support dog. A heat exchanger in the line maintained blood temperature at 37°C. A PE cannula was placed in the right ventricle via the superior vena cava to collect sinus blood flow, which was then returned to the support dog via femoral venous cannulas. Immediately after the cannula for cross-perfusion was opened the innominate artery, descending aorta, vena cava, and azygos vein were ligated. Perfusion was maintained at physiological pressures. At this point fibrillation of the heart was produced by an electric shock and the lungs were removed. The left atrium was widely opened and the chordae tendineae were cut. A 60-ml rubber balloon was placed in the cavity of the left ventricle through an apical stab wound and filled with a known volume of saline. Thus the heart beat isovolumically at constant end-diastolic volumes. Careful placement of the balloon prevented significant aortic regurgitation from retrograde perfusion, and perfusion pressure was monitored. The mitral valve was sutured and the orifice was occluded by a rubber stopper 2 cm in diameter which was tied into the mitral valve ring. Thesbian blood was drained from the left ventricle by a PE cannula inserted through a rubber stopper. The atroventricular bundle was divided through a right atriotomy, and pacing electrodes were placed on the distal portion. Left ventricular pressure (LVP) was continuously recorded at high and low sensitivity. The LVP was measured...
with a pressure transducer (Statham P23Db) through a short metal cannula, and was electrically differentiated (UD-20 Universal differentiator, Electronic Gear). Pressure curves could also be displayed on a storage oscilloscope and photographed directly. The ventricular pressure system had a natural frequency of 60-75 Hz ("pop test"), and was flat to at least 50 Hz. The differentiator was characterized by a phase lag of $90^\circ \pm 1^\circ$ to at least 120 Hz.

**PROTOCOL**

Control data were obtained during a period of perfusion at physiological mean aortic pressure (96 ± 3 mm Hg). Total mean perfusion pressure (PP) then was quickly reduced by opening lateral tube (A) (Fig. 1) placed at lower level of the perfusion line ($h_1$) and held constant at various levels (0-50 mm Hg) for periods of 1-6 minutes. PP then was allowed to return to the control level. Data were collected continuously throughout this period of hypoperfusion and the subsequent recovery period. Periods of hypoperfusion of any heart were not repeated until a stable state was obtained; this usually required 20-35 minutes. To prevent ventricular premature beats during recovery, heart rate was held constant at 180 beats/min during the entire experiment. At this heart rate incomplete ventricular relaxation was not observed.

**ISCHEMIA**

Results of a typical experiment are shown in Figure 2A, and the statistical analysis of 17 experiments in which a period of ischemia lasting 6 minutes was followed by a recovery period of 25 minutes is shown in Figure 2B. Following the onset of either ischemia or recovery, data were collected at intervals of 12 seconds for 3 minutes, and then after each minute. The data are presented as percentage changes ± 1 SE. Under control conditions, PP averaged 96 ± 3 mm Hg; coronary blood flow measured in eight experiments averaged 62.8 ± 6 ml/min; LVP, 110 ± 6 mm Hg; positive $dP/dt$, 2,250 ± 200 mm Hg/sec; negative $dP/dt$, 1,920 ± 160 mm Hg/sec; and left ventricular end-diastolic pressure (LVEDP), 8 ± 1 mm Hg. When the period of ischemia was induced, PP decreased to 50% of the control within 6 seconds and fell to 38 ± 3% of control at 36 seconds. It remained stable at this value for up to 6 minutes. Coronary blood flow fell to 25.1 ± 1.3% of control after 1 minute and to 36.9 ± 2.4% after 3 minutes, and it increased to 39.6 ± 1.7% at 5 minutes. LVP fell rapidly to 77.6 ± 1.95% of control after 12 seconds, to 63 ± 3% after 1 minute, and to 50 ± 5% after 6 minutes. Positive $dP/dt$ decreases at a slower rate than LVP, reaching 93.4 ± 1.22% of control after 12 seconds, 70 ± 3% after 1 minute, and 56 ± 5% after 6 minutes. The rate of relaxation as reflected by negative $dP/dt$ (LV - $dP/dt$) fell to 75.4 ± 2.2% of control after 12 seconds, 49 ± 4% after 1 minute, and 41 ± 4% after 6 minutes. These differences were all statistically significant ($P < 0.05$).

Specific changes in the course of the left ventricular contraction during ischemia are also shown in Figures 3A and 4A. Within 1 minute of ischemia, the fall in developed pressure was accompanied by a marked shortening in the time to peak (TTP) left ventricular pressure, with little change in $dP/dt$. After 2 minutes of ischemia, the $dP/dt$ fell while TTP was prolonged back toward control. In 13 experiments TTP fell from 157 ± 6 msec at control to 131 ± 5.5 msec after 30 seconds; at 5 minutes, TTP averaged 143 ± 6.5 msec (Fig. 4A).

The immediate change in LVP was not dependent on a reduction of $dP/dt$ alone (Fig. 5A), but was due largely to the decrease in TTP. However, this early decline in LVP was related temporarily to the decline in negative $dP/dt$ (Fig. 5B).

**RECOVERY FROM ISCHEMIA**

After 6 minutes of ischemia, PP was returned to the control ($h_1$) level by closing the lateral tube A placed at the lower level ($h_2$ level) of the perfusion line (Fig. 1). Although
the height of the perfusion column was the same as during control, the PP at the level of the heart was 87 ± 1% of the control. This increased pressure drop across a constant resistance indicates an increase in coronary flow above control levels. This pressure difference disappeared after 3 minutes (Fig. 2B); coronary blood flow measured for eight experiments increased to 117 ± 1% after 1 minute, 110 ± 2% after 3 minutes, and 104 ± 2% at 5 minutes. LVP quickly returned to control values after 36 seconds with an overshoot which reached 109 ± 4% of the control at 84 seconds, and then gradually declined to 90 ± 2% of control after 25 minutes of recovery. A similar but lower course was followed by positive dP/dt. However, the rate of relaxation remained depressed throughout the period of recovery.

In Figure 3B, LVP curves at 15, 30, and 60 seconds of recovery are displayed on a storage oscilloscope. During the initial phases of recovery, TTP became very prolonged and then gradually returned toward, but not to, control levels. The data for nine experiments are shown in Figure 4B and illustrate the initial overshoot in TTP followed by a gradual return to normal.

The effects of repeated episodes of ischemia are shown in Figure 6. Characteristically, the results were qualitatively similar to those obtained after the first episode of ischemia,
but the function was more depressed during subsequent episodes of ischemia and recovery. The overshoot of LVP and dP/dt during recovery persisted after multiple episodes of ischemia. Ultimately, the baseline attained subsequent to each episode of ischemia was progressively lower than the control. In studies on these control preparations in which ischemia was not produced, this decline in contractile activity did not occur in the same period of time.

Discussion

The force of myocardial contraction declines rapidly after the onset of hypoxia. Orias\textsuperscript{1} noted an immediate decrease in amplitude and duration of ventricular pressure development after ligation of a large coronary artery. Despite the widespread interest in the functional consequences of myocardial ischemia, the basic defects in the mechanics of contraction are poorly understood. Tyberg et al.\textsuperscript{7} studied cat papillary muscles and showed that hypoxia affected both the duration and velocity of contraction. However, the time course of the effects of hypoxia on these parameters of contraction could clearly be separated, suggesting that duration and velocity of contraction might involve different mechanisms, each of which was differentially affected by hypoxia. They attributed these abnormalities to alterations in excitation-contraction coupling.

In our present experiments on the intact heart, a rapid fall in force development was noted within seconds after the onset of ischemia. Initially this decline was due mainly to a

![Graph](image)
The results are illustrated as the mean ± SE pressure, and the overshoot during recovery persisted after multiple episodes of ischemia. Ultimately the baseline attained subsequent to the episodes of ischemia was progressively lower than the control. LVP during ischemia was directly related to the fall in perfusion pressure. The decrement in episodes of ischemia. The duration of contraction helps to maintain force development, albeit at levels below control. The reason for this disparity in results is not clear.

In studies on the papillary muscle, Tyberg et al. noted that during the period of recovery from hypoxia, changes in velocity and duration of contraction were most marked. They noted a prompt return in the duration of contraction to and beyond control with the peak overshoot occurring after 2-5 minutes of reoxygenation. Rate of force development also recovered, but less rapidly than TTP, and demonstrated no overshoot. Thus, the fairly prompt, although incomplete, recovery of force development was due primarily to the increase in the duration and not the velocity of contraction. Rate of relaxation, already decreased during hypoxia, became more markedly decreased during early recovery from hypoxia and then gradually returned toward control.

During recovery from ischemia, findings for the intact hearts did not directly parallel those in papillary muscles. Duration of contraction of the intact heart became prolonged during early reoxygenation and contributed importantly to recovery of force development; this change is similar to findings for papillary muscles. However, in the intact hearts the rate of force development recovered very promptly and reached values above controls within 30 seconds after restoration of perfusion, whereas in papillary muscles it recovered slowly and incompletely. Thus, LVP reached values significantly above control as a result of increases in both duration and velocity of contraction. The further decrease in the rate of relaxation during early recovery in papillary muscles was not seen in intact hearts. Again, the reasons for the divergence of findings for papillary muscles and intact hearts are not certain.

Alterations in relaxation are of interest because they may affect the course of ventricular filling. With the onset of ischemia, a reduction in the velocity of relaxation occurs and could contribute to early alterations in apparent compliance of the ventricle during acute ischemia. With cessation of the ischemic period, the rate of relaxation remains low and may contribute to persistent restriction of early ventricular filling. Such alterations in relaxation, together with changes in the course of pressure development, also may form the basis for asynchronous contraction and relaxation in the segmentally ischemic heart. The rapidity with which alterations in contractile activity occur during ischemia has suggested abnormalities of excitation-contraction coupling.

The rate of pressure development (dP/dt) is a function of the velocity of contractile element shortening and the elastic properties of noncontracting elements in the ventricular wall. This parameter appears to be a very sensitive index of changes in myocardial contractility, but does not change early after the onset of ischemia, as shown by the present study. This reflects the dissociation observed between force and velocity during the course of ischemia and its recovery phase. Previous studies have indicated that changes in dP/dt during ischemia are due to alterations in contractile element behavior rather than to changes in series elasticity.
The underlying biochemical alterations that produce these changes in mechanical function are poorly understood. Many other factors which are known to alter myocardial contractility, such as pH, temperature, and ionic changes, may be involved in the alteration of these events. Early in hypoxia, changes in high energy phosphates occur too slowly to explain an immediate change in contractile activity. The function of the sarcoplasmic reticulum is not significantly depressed early in hypoxia, although intracellular H+ may compete with Ca2+ for binding to troponin. The relaxation rate diminishes fairly early. Relaxation is a complex event, but the observed changes could result from either a combination of a decreased rate of cleavage of Ca2+ from the troponin complex and depressed binding by SR or depressed rates of pumping by the sarcoplasmic reticulum. Duration of contraction, initially abbreviated, may increase later as the relaxation system becomes depressed and increasing amounts of Ca2+ may accumulate in proximity to the contractile system. Some inward diffusion of Ca2+ across the cell membrane, made "leaky" by the hypoxia, might also play a role late in hypoxia.

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References

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