Effects of Acute Regional Myocardial Ischemia on Left Ventricular Function in Dogs

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ABSTRACT

The immediate functional deficit resulting from acute regional myocardial ischemia was evaluated in 40 anesthetized dogs. Ventricular function curves, maximum dp/dt, isovolumetric force-velocity curves, and peak systolic and resting diastolic length-tension curves were assessed at fixed heart rate and constant aortic pressure before and during occlusion of the anterior descending coronary artery 2 to 3 cm distal to its origin. Mild, moderate, or marked depression of the ventricular function resulted from occlusion of the anterior descending artery, depending upon the anatomy of the intercoronary collateral vessels. Maximum loss of function was apparent 2 minutes after occlusion, and was quantitatively reproducible by reocclusion after an intervening period of unobstructed flow. Resting diastolic length-tension relations were not significantly altered by occlusion of the anterior descending artery. In 12 dogs, force-velocity relations were determined during the inscription of ventricular function curves and in every instance when depressed function was evident from the ventricular function curve, the simultaneously determined force-velocity curve also demonstrated impaired performance. At low preload levels, however, the force-velocity curves inscribed before and during occlusion of the anterior descending artery were not very dissimilar; with increasing ventricular volumes, the force-velocity curve inscribed during coronary artery occlusion progressively shifted downward and to the left of the control curve. Maximum velocity, however, appeared to be unchanged suggesting that this index of contractility is not a satisfactory method for assessing cardiac performance during acute regional myocardial ischemia.

ADDITIONAL KEY WORDS

intercoronary collateral vessels force-velocity relations contractility coronary artery occlusion

The effects of acute regional myocardial ischemia on left ventricular function have not been precisely defined, even though occlusion of the artery was produced experimentally in the dog by Chirac as long ago as the seventeenth century. Porter in 1896 (1) and Miller and Matthews in 1909 (2) observed that a fall in systemic blood pressure and arrhythmias followed occlusion of the anterior descending branch of the left coronary artery in dogs. More recent studies have assessed the functional deficit resulting from generalized myocardial ischemia produced by reducing flow into the coronary arteries (3) or by the embolization of small particles into the coronary circulation (4-7). The functional capacity of the heart has also been evaluated several days after the experimental production of myocardial infarction (8), but further information is needed regarding the immediate effects of acute regional myocardial ischemia on left ventricular function. Assessments of the immediate functional deficit resulting from occlusion of the anterior descending coronary artery were therefore performed in dogs, and the results are described in this report.

Methods

Forty mongrel dogs weighing 19 to 28 kg were anesthetized with pentobarbital (35 mg/kg iv). A cuffed endotracheal tube was inserted, and ventilation was maintained by
FIGURE 1

Schematic representation of the cannulations and extracorporeal circuit employed to obtain left ventricular function curves. Aortic pressure and heart rate were maintained constant. Force-velocity relations were simultaneously determined from isovolumetric beats obtained by momentarily occluding the ascending aorta while ventricular function curves were being done.

Ao = aorta; PA = pulmonary artery; LA = left atrium; RV = right ventricle; RA = right atrium; LV = left ventricle; LVED = left ventricular end-diastolic pressure; Ven. Res. = venous reservoir; SG = strain gauge.

a positive-pressure respirator supplying oxygen. The thorax was opened widely, and heparin (3 mg/kg) was administered intravenously. Blood temperature was monitored by a thermistor in the inferior vena cava and maintained at 37°C by a heat exchanger in the extracorporeal circuit. The sinoatrial node was crushed and the heart rate maintained constant by electrical stimulation of the right atrium at a rate of 170 beats/min. The extracorporeal circuits were primed with fresh, heparinized homologous blood.

VENTRICULAR FUNCTION STUDIES

In 23 dogs, the various cannulations shown schematically in Figure 1 were carried out. Left ventricular function curves were obtained by diverting all systemic and coronary venous return to a reservoir, and returning it through a roller pump to the main pulmonary artery. A Y-shaped cannula at the left ventricular apex permitted the simultaneous measurement of the left ventricular end-diastolic pressure and the full left ventricular pressure pulse (Statham P23Db strain gauges), from which the first derivative (Maximum dp/dt) was electronically calculated by an R-C differentiating circuit. Pulmonary arterial inflow was monitored by a calibrated electromagnetic flow probe (Model E-3000, Medicon Company, Los Angeles, California) placed in the line returning blood to the animal. Left ventricular output was increased stepwise as left ventricular and aortic pressures were continuously recorded until a left ventricular output of 5500 ml/min was achieved or the left ventricular end-diastolic pressure exceeded 25 mm Hg. Aortic pressure was maintained constant during the study by infusing or withdrawing arterial blood through cannulas inserted into both femoral and carotid vessels. Left ventricular function curves were determined by relating left ventricular stroke work to the left ventricular end-diastolic pressure. Left ventricular stroke work was calculated from the equation:

\[ LVSW = SV \times \frac{(Aop - LVED)}{100} \]

where

LVSW = left ventricular stroke work (g-m),
Aop = mean aortic pressure (cm H2O), LVED

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The left anterior descending coronary artery was then occluded with a bulldog clamp 2 to 3 cm distal to its origin and just proximal to the largest branch traversing the anterior surface of the left ventricle. Two minutes thereafter, while the artery remained occluded, a second ventricular function curve was inscribed. Anterior descending flow was restored, and after a 20-minute period, the anterior descending artery was again occluded and 2 minutes thereafter, a third ventricular function curve was inscribed. After completion of this curve, anterior descending flow was restored and 10 minutes thereafter, a fourth or final control curve was obtained. Each period of unobstructed flow, the anterior descending flow was restored, and after a 20-minute period, the anterior descending artery was again occluded and the evaluation sequence was resumed.

FORCE-VELOCITY AND LENGTH-TENSION STUDIES

In 12 dogs, while ventricular function curves were being done, the ascending aorta was momentarily occluded in diastole with a vascular clamp and an isovolumetric ventricular contraction obtained. A left ventricular flow rate was selected so that isovolumetric beats were obtained both before and during coronary artery occlusion at similar left ventricular end-diastolic pressures. Left ventricular dp/dt was simultaneously recorded. Ventricular volume was determined from passive pressure-volume curves inscribed immediately after the conclusion of each experiment. These data were used to determine force-velocity relations simultaneously with the inscription of ventricular function curves.

In 17 additional dogs, cardiopulmonary bypass was maintained at a flow rate sufficient to maintain mean aortic pressure at 100 mm Hg. Isovolumetric left ventricular contractions were obtained by inserting a latex balloon attached to a metal cannula into the cavity of the left ventricle through a stab incision at its apex. Ventricular volume was established by inflating the balloon with a measured volume of saline solution. Left atriotomy was performed, and the mitral valve orifice was occluded with a fenestrated plug which also drained coronary blood returning directly to the left ventricular cavity. A purse-string suture positioned and secured the plug in the mitral annulus, and any pulmonary venous blood was aspirated through the atriotomy with a cardiomyococcytus and returned through the venous reservoir. At constant aortic pressure and fixed heart rate, this preparation provided data from which force-velocity curves and length-tension curves could be constructed. Each of these curves was determined before and 2 minutes after occlusion of the anterior descending coronary artery. Left ventricular end-diastolic pressure, the full left ventricular pressure pulse, and the first derivative of left ventricular pressure (dp/dt) were simultaneously recorded as the volume of the intraventricular balloon was increased to 25 ml in 5-ml increments. Resting diastolic and peak systolic length-tension curves were inscribed by plotting the peak systolic or resting diastolic force versus the increase in internal ventricular radius. The ventricle was assumed to be a thick-walled sphere. The total tangential wall force at the endocardial equator by the La Place relationship is $p r_0^2$. Assuming that this force is evenly distributed across the surface area of a thick-walled sphere ($4\pi r^2$), then wall stress or force per unit area is given by

$$\text{Force} = \frac{Pr_0^2}{(r_0^2 - r_i^2)} \times 1.39,$$

where $P$ is force (g-wt/cm$^2$)$^1$, $F$ is peak systolic left ventricular pressure or left ventricular end-diastolic pressure (mm Hg), $r_0$ is the internal (endocardial) ventricular radius (cm), $r_i$ is the external epicardial radius (cm), and 1.36 is a conversion factor (9). Since the ventricle was assumed to be a sphere, $r_0$ and $r_i$ were solved from the equation

$$\text{Volume} = \frac{4}{3}\pi r^3.$$

The internal ventricular radius was determined from the volume of the left ventricular balloon and the external radius from the sum of the volumes of the left ventricular balloon and the left ventricular muscle mass (10, 11). The specific gravity of the left ventricular muscle mass was assumed to be one (9-12), and the left ventricular muscle volume was therefore determined by its weight. By assuming a left ventricular spherical model rather than a prolate spheroid of equal volume (major-minor axis 2:1), the base-to-apex fiber length is equal to the

\footnote{Force defines the energy of a mass in a gravitational field. The gram is a mass unit. When used to define a force, the gram is correctly noted as grams force (g-f) or gram weights (g-wt) indicating that gravitational field is an included value, which, therefore, allows translation to conventional force units (i.e., dynes or atmospheres).}
The relative error between the two systems in calculating force is 8% (12). Since no geometrical model duplicates ventricular dimensions, the necessity of assuming a model for force calculations implies the comparison of relative rather than absolute values.

Force-velocity curves were inscribed by determining the instantaneous relations between force and velocity of the contractile element at 10-msec intervals during the course of single isovolumetric beats. Force was determined as described above except that instantaneous left ventricular pressure was substituted for peak systolic left ventricular pressure in the force formula. Velocity was calculated from the equation

$$VCE = \frac{dp}{dt} \times \frac{2\pi r(t_{max})}{P}$$

where $VCE$ is velocity of the contractile element (cm/sec) and $P$ is ventricular pressure (mm Hg) (10). The computations were facilitated by a digital computer.

In six dogs the rate of loss of function after occlusion of the anterior descending artery was also assessed by relating the change in peak systolic force to time.

**Results**

**Ventricular Function Studies**

In 15 of the 23 dogs in which four consecutive ventricular function curves were inscribed before (curve 1), during (curve 2 and 3) and after (curve 4) occlusion of the left anterior descending coronary artery. Each panel shows the function curves inscribed in a representative animal from each group. (See text.) LVSW = left ventricular stroke work, LVED = left ventricular end-diastolic pressure.
inscribed, the initial and final control function curves were similar and showed no depression of ventricular function; the two curves inscribed during occlusion of the left anterior descending artery were also similar and demonstrated moderate or severe depression of ventricular function (Fig. 2, A). In three dogs, both curves inscribed during occlusion of the left anterior descending artery, as well as the final control curve, were similar and demonstrated moderate or severe depression of ventricular function (Fig. 2, B). In three dogs (Fig. 2, C), ventricular fibrillation prevented the inscription of ventricular function curves after occlusion of the anterior descending artery, and in two dogs (Fig. 2, D), only mild alterations in ventricular function resulted from occlusion of the anterior descending artery. In both of these animals, a large posterior interventricular artery anastomosed with the left anterior descending artery.

Measurements of maximum dp/dt paralleled the findings demonstrated by the ventricular function curves, and the decline that was apparent following occlusion of the anterior descending artery was also quantitatively reproducible by reocclusion of the coronary artery after an intervening period of unobstructed flow.

**FORCE VELOCITY AND LENGTH TENSION STUDIES**

The 12 animals in which force-velocity curves were determined simultaneously with the inscription of ventricular function curves provided data for the comparison of these two methods of assessment of cardiac function. Typical ventricular function curves and force-velocity curves inscribed in the same animal before and during occlusion of the anterior descending artery are reproduced in Figure 3. In every animal in which a functional deficit was evident on the ventricular function curve.
inscribed during occlusion of the anterior descending artery, the simultaneously inscribed force-velocity curve also demonstrated impaired function. In each animal there were decreases in maximum developed force and decreases in velocity at forces greater than 40 g-wt. However, the maximum measured velocity and its extrapolation by eye to maximum velocity did not change after occlusion of the anterior descending artery. It should be pointed out, however, that the determination of maximum velocity by extrapolation is a somewhat unreliable technique.

Six of the dogs in which isovolumetric contractions were obtained from an intraventricular balloon provided data regarding the rate of loss of function after occlusion of the anterior descending artery. The results of a typical experiment in which the peak systolic isometric force generated was related to time after coronary artery occlusion are illustrated in Figure 4. There was a prompt decline in peak systolic isometric force after coronary artery occlusion and maximum loss of function was apparent 2 minutes after occlusion. Typical length-tension and force-velocity curves constructed from data obtained from the intraventricular balloon preparation in an animal before and 2 minutes after occlusion of the anterior descending artery are reproduced in Figure 5. At any given ventricular radius or myocardial fiber length, resting diastolic tension was the same before and after coronary artery occlusion. However, at any given ventricular radius or myocardial fiber length, a decrease in peak isometric systolic force was apparent after occlusion of the anterior descending artery when compared to the tension developed at the same fiber length before coronary artery occlusion. In each animal, the force-velocity curve inscribed during coronary artery occlusion was shifted downward and to the left compared to the curve inscribed in the same animal at the same ventricular volume before coronary artery occlusion. This shift was greater at larger ventricular volumes, that is, at higher preload levels the injury produced by occlusion of the anterior descending artery was more prominently displayed. The curves tended to converge and at low force levels the maximum measured velocity was similar before and after occlusion of the anterior descending artery.

Discussion

In the present study four consecutive ventricular function curves were inscribed in the same animal over a 70- to 90-minute period by a right heart bypass preparation which permitted the independent control of mean aortic pressure, heart rate, and left ventricular stroke volume. Assessments of the rate of loss of function after occlusion of the descending artery demonstrated that maximum loss of function was apparent 2 minutes after occlusion, and therefore the function curves were initiated 2 minutes after flow in the descending artery was interrupted. The degree of depression of ventricular function resulting from the occlusion depended on the anatomy of the intercoronary collateral vessels. When a large anastomosis was present.
FIGURE 3

A: Typical peak systolic and resting diastolic length-tension curves constructed from isovolumetric left ventricular contractions obtained from an intraventricular balloon. Impaired ability to generate force is apparent during coronary occlusion (ischemia). Resting diastolic tension is not changed by coronary occlusion.

B: Force-velocity curves inscribed in the same dog at different ventricular volumes (preload). The force-velocity curve inscribed during coronary artery occlusion is shifted downward and to the left compared to the curve inscribed at the same ventricular volume before coronary artery occlusion. This shift is greater at larger ventricular volumes. LV vol = left ventricular volume.

The ventricular function curve technique for assessing cardiac performance assumes that ventricular diastolic compliance is unaltered, since left ventricular end-diastolic pressure is used as an index of myocardial fiber length. In the present studies, the ischemia produced by occlusion of the anterior descending artery 2 to 3 cm distal to its origin did not alter left ventricular diastolic compliance when assessed by resting diastolic length-tension relations. Thus the depression of function apparent from the ventricular function curves was a valid indicator of the magnitude of the functional impairment produced by the ischemia. The length-tension curves inscribed by plotting peak systolic isometric force versus the increase in ventricular radius display the functional deficit in a manner very similar to the ventricular function curves, except that in these studies...
ventricular volume or myocardial fiber length is determined by the known and variable volume of the intraventricular balloon.

Implied in the comparison of force-velocity curves determined before and after an intervention is the assumption that the series elastic elements of the myocardium are not changed. Alterations of the series elastic may result, however, from regional ischemia since the elasticity of the contractile units defunctionalized directly by the ischemia or indirectly by asynchrony of contraction may summate with the elasticity of the existing series elastic components. Changes in series elasticity would be reflected by a change in the constant 28, and hence lead to errors in determining the velocity of contractile element and invalidate the use of the force-velocity technique for the assessment of the functional deficit produced by regional myocardial ischemia. Although no assessment of the effects of ischemia on the series elastic components was made in the present experiments, Forward et al. (13) detected no change in the series elastic component during regional ischemia. Further studies in this regard, however, would be of interest. In addition, accurately determining maximum velocity by the extrapolated intersection of the force-velocity curve with the velocity axis can be very difficult and this is an important defect in the use of maximum velocity as an index of contractility. In spite of these sound theoretical objections to the use of the isovolumetric force-velocity technique as a method of assessment of cardiac performance during acute regional myocardial ischemia, results in the animals in which force-velocity relations were determined only at small ventricular volumes, or low preload levels, the severity of the functional deficit might not be appreciated. This would suggest that the state of the contractile element is unchanged by occlusion of the anterior descending artery, but that the number of contractile sites is decreased. When larger forces are encountered, the deficit in the number of contractile sites participating in the generation of force becomes more apparent.

References
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