Left Ventricular End-Diastolic Pressure Volume Relationships with Experimental Acute Global Ischemia

IGOR PALACIOS, M.D., ROBERT A. JOHNSON, M.D., JOHN B. NEWELL, B.A.,
AND WM. JOHN POWELL, JR., M.D.

SUMMARY The mechanism of elevation of left ventricular end-diastolic pressure during acute global ischemia was evaluated by examination of the relative contributions of a decrease in contractility and an alteration of the pressure-volume relationship. The external circumference (mercury-in-silastic gauge) pressure relationship, as an index of the pressure-volume relationship, was studied in beta adrenergic and ganglionic blocked, open chest dogs on right heart bypass at constant heart rate and aortic pressure. Ischemia of one and two hours' duration was produced by reducing total coronary blood flow in cannulated left and right coronary arteries until left ventricular end-diastolic pressure rose significantly. At a constant stroke work, left ventricular end-diastolic pressure rose from 5.0 ± 0.5 to 15.0 ± 0.5 cm H2O in the experiments of one hour of ischemia, and from 7.0 ± 1.0 to 17.0 ± 1.0 cm H2O in experiments of two hours of ischemia. Ischemia was followed by one hour of restoration of coronary blood flow. Ischemia produced a marked depression of ventricular function: stroke work, considered at a left ventricular end-diastolic pressure of 15 cm H2O, decreased from 21.0 ± 3.0 to 3.5 ± 0.5 gm-m, and from 15.0 ± 2.0 to 2.5 ± 0.5 gm-m, in the experiments of one and two hours, respectively. Neither ischemia nor reflow changed the pressure-volume relationship. Thus, the elevation of left ventricular end-diastolic pressure during ischemia in an otherwise normal canine myocardium is due to a decrease in systolic performance of the heart rather than to an alteration of the pressure-volume relationship.

LEFT VENTRICULAR END-DIASTOLIC PRESSURE (LVEDP) is determined by volume and pressure load conditions, systolic performance of the heart, and diastolic pressure-volume relationships. Left ventricular end-diastolic pressure increases during angina in some patients with coronary artery disease. The mechanism of this increase, whether a decrease in left ventricular contractility or an alteration in pressure-volume relationship, remains controversial.

The present experiments were designed to examine the mechanism of elevation of end-diastolic pressure during acute left ventricular ischemia in an otherwise normal heart. A canine model was employed. Pressure-external circumference relationships were studied before, during, and after left ventricular ischemia. Global left ventricular ischemia, produced by a controlled reduction in flow in both coronary arteries, was used because local ischemia may obscure the relative contribution of normal and ischemic myocardium to the overall pressure-circumference relationship, when the circumferential gauge surrounds both ischemic and nonischemic myocardium. Also, overall intracavitary pressure may not reflect end-diastolic tension of a local ischemic area.

Methods

1. Right Heart Bypass

Right heart bypass preparation (fig. 1) experiments were conducted in 13 open chest mongrel dogs weighing between 17 and 20 kg. The dogs were anesthetized intravenously with a mixture of chloralose (60 mg/kg) and urethane (600 mg/kg). The trachea was intubated and ventilation was maintained with a Harvard respiratory pump using 100% oxygen. Details of the right heart bypass preparation have been previously reported. Both left main and right coronary arteries were cannulated and total coronary blood flow was controlled by means of a separate calibrated roller pump. Total coronary venous blood flow was measured directly from the cannulated right ventricle.

Heart rate was maintained constant throughout the experiments by means of atrial pacing after sinoatrial node crush. The aorta was cannulated at the junction of thoracic and abdominal segments. Mean aortic pressure in the
thoracic aorta was kept constant by pumping or withdrawing blood through the cannula placed in the lower thoracic descending aorta. Blood was pumped to an overflow column which was connected to both femoral arteries in order to keep the arterial pressure constant in the abdominal vascular bed so as to preserve kidney and liver function. The heart rate and mean aortic pressure utilized in the right heart bypass preparation are shown in table 1. A short Y-shaped metal cannula was inserted into the left ventricle through the apex in order to measure peak left ventricular pressure and left ventricular end-diastolic pressure (LVEDP). Pressures were measured in the aorta, left ventricle and coronary cannula by means of Statham P23Db pressure transducers. The rate of rise of left ventricular pressure (LV dP/dt) was recorded electronically and calibrated as previously described.5, 6

Left ventricular end-diastolic circumference and base-to-apex left ventricular length were measured by using mercury-in-silastic gauges.6 The circumferential gauge was placed around the equator of the left ventricle, including the interventricular septum. The ends of the gauge were sutured to the ventricular wall. In order to avoid vertical displacement, three loose sutures were placed at equidistant points along the gauge. In five experiments a 7 cm base-to-apex gauge was positioned on the anterior wall of the left ventricle parallel to the left anterior descending artery. It was fixed to the left ventricular wall in a way similar to that described above for the circumferential gauge. The gauges were connected to a modified electronic Wheatstone bridge yielding an output representative of left ventricular end-diastolic circumference and base-to-apex left ventricular length. The gauges were calibrated prior to, and subsequent to, each experiment by recording the deflection produced as the gauge was stretched and subsequently shortened against a centimeter ruler. The calibration of each gauge was the same at the beginning and at the end of each experiment, i.e., there was no drift of the gauges over time.

Blood from donor dogs was thoroughly mixed with that of the experimental animal prior to the experimental period. Blood of the extracorporeal circuit was directed through a bubble oxygenator with a gas mixture of 97% O₂ and 3% CO₂. All dogs were systemically anticoagulated with heparin.

![Figure 1. Right heart bypass preparation (RHBP). Arrows indicate the direction of flow. Circumferentially and vertically oriented length gauges are shown on the left ventricle. Abbreviations: S.G. = strain gauge; E = electrode; LCA = left main coronary artery; RCA = right coronary artery.](image)

### Table 1. Heart Rate, Mean Systemic Pressure, Coronary Flow and Perfusion Pressure, and Duration of Ischemia

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*Pressures and flow were taken at the end of each period, N = 15.
An epicardial electrocardiogram was obtained from an electrode sutured on the surface of the left ventricle. All the variables were recorded on an eight channel Hewlett Packard direct writing recorder at 25 and 100 mm/sec paper speed.

When the right heart bypass preparation achieved a steady state, the dogs were beta adrenergically and ganglionically blocked with propranolol (0.5 mg/kg) and mecamylamine (5 mg/kg). The adequacy of the beta blockade was documented with Isuprel (3–4 gamma) added to the reservoir at the beginning, middle and end of each experiment. After a new steady state was achieved, the cardiac output was raised in increments by increasing the output of the blood flow pumping through the main pulmonary artery. Pressures were plotted against left ventricular end-diastolic circumferenced and base-to-apex left ventricular length to obtain curves which were defined as pressure-length relationships (control state). Ventricular function curves were obtained plotting left ventricular stroke work against LVEDP. Mean coronary pressure during the control period and during restoration of coronary blood flow was maintained at the level of the mean aortic pressure.

Subsequent to obtaining the control curves, acute global left ventricular ischemia was produced by reducing total coronary blood flow until LVEDP rose significantly. The coronary pressures and flows during ischemia are shown in table 1. Coronary blood flow and cardiac output were kept constant throughout the ischemic period. Ischemia was produced for a period of one hour in four experiments and for a period of two hours in five experiments (experiments numbered 1 through 9 in table 1).

Pressure-circumference and ventricular function curves were obtained as above during early ischemia (8 minutes) and every 30 minutes during the remainder of the ischemic period. At the end of the ischemic period coronary blood flow was increased until the control level of mean coronary pressure was achieved (table 1). The restoration of coronary blood flow period lasted 60 minutes. During this period pressure-circumference relationships and ventricular function curves were obtained at early restoration of flow (10 minutes) and later restoration of flow (60 minutes).

In two experiments two successive periods of ischemia, each one followed by one half hour of restoration of coronary blood flow, were performed. In these experiments the pressure-circumference relationships and ventricular function curves were obtained at the same time in the same way described above during ischemia and restoration of coronary blood flow (experiments numbered 10 and 11 in table 1).

Finally, two control experiments in nonischemic hearts were carried out. In these experiments the pressure-circumference relationship and ventricular function curve were obtained every 30 minutes for a period of three hours (experiments numbered 12 and 13 in table 1).

2. The Isovolumic Left Ventricular Preparation

Two experiments were conducted in two (fig. 2) dogs in which the isovolumic left ventricular preparation was employed. Details of this preparation have been reported previously. A distensible latex balloon was placed in the left ventricle through the mitral valve and affixed to the tip of a "Y" shaped cannula in order to measure left ventricular end-diastolic pressure and peak left ventricular pressure. The balloon was filled with a known amount of saline solution, which was constant during each experiment. Drains were placed in both the left atrium and the left ventricle between the ventricular wall and the balloon. Mean aortic pressure was kept constant at a level higher than the peak developed left ventricular pressure to prevent herniation of the balloon through the aortic valve.

The cannulation of the left main and right coronary arteries, placement of the external circumference gauge, recording of the variables, and beta adrenergic and ganglion blockade were conducted as previously described in the right heart bypass preparation. The heart rate and mean aortic pressure utilized in the two isovolumic left ventricular preparations are shown in table 1.

In these experiments, acute global left ventricular ischemia was produced by reducing total coronary blood flow until peak left ventricular pressure and LV dP/dt decreased significantly. Coronary blood flow was kept constant throughout the two hour ischemic period. Ischemia was followed by one hour of restoration of flow as described above.

3. Statistical Analysis

F-tests were used to compare ischemic with control pressure-circumference relationship. The F statistic is the ratio of two estimates of variance and is used to test the hypothesis that the two variances are equal. T-tests were used to compare ischemic with control LVEDP (at constant
stroke work), and ischemic with control stroke work (at constant LVEDP). Exponential functions were fit to the control pressure-volume relationships with a nonlinear regression program.

Results

1. Experimental Data

1. Experiments with a One Hour Ischemic Period

Figure 3 shows the results of four right heart bypass preparations in which ischemia was produced for a period of one hour followed by restoration of coronary blood flow for one hour. The pressure-circumference relationship of the left ventricle did not change with acute global ischemia (8, 30, 60 minutes) or with restoration of coronary blood flow (10, 60 minutes).

It can be seen in figure 4 that ischemia resulted in substantial changes in left ventricular end-diastolic pressure for a given stroke work and in stroke work for a given left ventricular end-diastolic pressure. Left ventricular end-diastolic pressure increased significantly from 5.0 ± 0.5 (SEM) to 15.0 ± 0.5 cm H2O at a stroke work of 3 gm-m. Stroke work decreased significantly from 21.0 ± 3.0 gm-m to 3.5 ± 0.5 gm-m at a left ventricular end-diastolic pressure of 15 cm H2O. Left ventricular dP/dt decreased from 2350 ± 560 mm Hg/sec to 1000 ± 180 mm Hg/sec at a left ventricular end-diastolic pressure of 15 cm H2O (P < 0.05).

Restoration of coronary blood flow resulted in a significant decrease of LVEDP from 15.0 ± 0.5 to 9.0 ± 1.0 cm H2O at a stroke work of 3 gm-m. There was an increase in stroke work from 3.5 ± 0.5 to 13.8 ± 4.0 gm-m at an LVEDP of 15 cm H2O; this change did not reach significance because of wide scatter of the values, although stroke work increased in each experiment.

2. Experiments with a Two Hour Ischemic Period

Figure 5 shows the results of five right heart bypass preparations in which ischemia was produced for a period of two hours followed by restoration of coronary blood flow for 60 minutes. Neither acute global ischemia nor return of flow altered the pressure-circumference relationship of the left ventricle during the 120 minutes of observation. Similarly, the early diastolic pressure-circumference relationship at the lowest point in LV pressure did not shift. Thus, the presence of complete relaxation at end diastole was confirmed.

The mean changes in these experiments in LVEDP and stroke work produced by ischemia of two hours' duration are exhibited in figure 6. Ischemia produced a significant increase in LVEDP from 7 ± 1 to 17 ± 1 cm H2O at a stroke work of 3 gm-m and a decrease in stroke work from 15.0 ± 2.0 to 2.5 ± 0.5 gm-m at an LVEDP of 15 cm H2O. Restoration of coronary blood flow produced a significant decrease in LVEDP from 17.0 ± 1.0 to 11.0 ± 1.0 cm H2O at a stroke work of 3 gm-m and a significant increase in stroke work from 2.5 ± 0.5 to 5.9 ± 1.0 gm-m at 15 cm H2O.

Figure 7 shows the pressure-base-to-apex length relationships of four right heart bypass experiments in which left ventricular end-diastolic circumference and base-to-apex length were determined simultaneously by means of two gauges placed perpendicular to each other. In these experiments the duration of ischemia was two hours. The corresponding left ventricular end-diastolic pressure-circumference relationships of each one of these right heart bypass preparations were shown previously in figure 5. Left ventricular end-diastolic pressure-base-to-apex length relationships did not change during either ischemia or restoration of coronary blood flow.

**FIGURE 3.** Pressure-circumference relationship of four RHBP experiments in which ischemia was produced for one hour followed by one hour of restoration of coronary blood flow (reflow). Abbreviations: LVEDP = left ventricular end-diastolic pressure; LVEDC = left ventricular end-diastolic circumference.

**FIGURE 4.** Mean changes of left ventricular end-diastolic pressure and stroke work of four RHBP experiments in which ischemia was produced for one hour followed by one hour of restoration of flow. Abbreviations: S.W. = stroke work; C = control; I = ischemia; R = reflow. Other abbreviations as in figure 3. Brackets in this and in all subsequent figures, and in the text, refer to the standard error of the mean.
3. Experiments with Two Successive Periods of One Hour of Ischemia

Two successive periods of one hour of ischemia, each one followed by one half hour of restoration of coronary blood flow, failed to alter the end-diastolic pressure-circumference relationship. The data in figure 8 demonstrate the end-diastolic pressure-circumference relationship from one of these two hearts. A similar lack of change in this relationship was present in the other heart. In these two hearts the left ventricular end-diastolic pressures during pre-ischemia, ischemia, reflow and repeat ischemia were 5, 13, 9, and 17 cm H2O and 3, 16, 7, and 18 cm H2O, respectively, at a stroke work of 3 gm-m. In the same two hearts the stroke work during pre-ischemia, ischemia, reflow, and repeat ischemia was 38, 3, 23, and 2 gm-m and 16, 4, 10, and 2 gm-m, respectively, at a left ventricular end-diastolic pressure of 15 cm H2O.

4. Control Experiments

The end-diastolic pressure-circumference relationships for two control nonischemic hearts are shown in figure 9; there were no alterations over 3 hours. This excluded the possibility of nonischemic pressure-circumference relationship alterations in the right heart bypass preparation, which might have interfered with the interpretation of results during ischemia or restoration of flow.

5. Left Ventricular Isovolumic Experiments

Results of the two isovolumic left ventricular experiments are exhibited in figure 10. It can be seen that LVEDP and left ventricular end-diastolic circumference were unchanged at the end of two hours of ischemia and one hour of restoration of coronary blood flow, indicating no alterations in the pressure-volume relationship and the pressure-circumference relationship.

II. Statistical Analysis

In addition to visual examination of the data, all ischemic left ventricular end-diastolic pressure-circumference relationships were statistically compared with the pressure-circumference relationships obtained in the corresponding
control periods. The comparison was based upon the demonstrated exponential relationship between pressure and volume at end-diastole.\(^\text{11}\) Volume ratios were estimated using cubed circumferences in place of volume. Provided left ventricular end-diastolic shape during ischemia or restoration of flow did not alter appreciably from that during the control period, the ratios of cubed circumferences can be substituted in the exponential pressure-volume relationship. The empirical considerations which underlie this use of cubed circumferences in place of volumes are discussed later. Ventricular wall thickness is not a factor in the comparison, since new absolute parameters, such as volume compliance, are not being derived; instead, the control pressure-volume relationship and ischemic pressure-volume relationship are being compared for the same ventricle.

The variance of the observed ischemic pressures about the computed pressure-volume curve which best fit the data was compared with the variance of the pressures observed in the control period about the same best fit curve. The resulting F statistic was consistent with the hypothesis that all the observations made during ischemia were samples from the same pressure-volume curve as that estimated from the control observations. Consequently, the parameters characterizing the pressure-volume relationship must remain unaltered by ischemia. Similarly, the pressure-volume relationship was unaltered by reflow. A more extensive derivation of equations which allow statistical analysis is given in the Appendix.

**Discussion**

The present data show that periods of acute global ischemia do not alter the circumference-pressure relationships of the canine left ventricle. Acute global ischemia was sufficient to produce a substantial elevation of the left ventricular end-diastolic pressure (LVEDP) and a marked decrease in both stroke work and LV dP/dt. The changes in LVEDP were always accompanied by changes in left ventricular end-diastolic circumference along the same pressure-circumference curve. This was also true during the period of restoration of coronary blood flow.
Left ventricular end-diastolic external circumference reflects end-diastolic muscle fiber lengths in the myocardium underlying the gauge. The constancy of the pressure-circumference relationship of the ejecting left ventricle during ischemia and restoration of coronary blood flow suggests that there were no changes in the pressure-volume relationship occurring during these periods. However, factors during ischemia or restoration of coronary blood flow which might interfere with the correlation of the pressure-circumference relationship to the pressure-volume relationship, e.g., changes in the shape or in the wall thickness of the left ventricle, should be considered. The possible contribution of shape changes was examined in these experiments in which both left ventricular end-diastolic circumference and base-to-apex left ventricular length were measured simultaneously. These experiments showed that when left ventricular end-diastolic circumference increased secondary to either ischemia or volume loading, base-to-apex left ventricular length also increased and the relationship of each of these two lengths to pressure remained the same. Therefore, changes in shape occurring during ischemia must be similar to changes in shape occurring during nonischemic volume loading. Thus, with regard to left ventricular shape, the pressure-circumference relationship should bear the same relation to the pressure-volume relationship under both conditions.

The possibility that the relationship of the pressure-circumference curve to the pressure volume curve was distorted by a change in left ventricular wall thickness was evaluated by two left ventricular isovolumetric experiments. Under these conditions, ischemia induced a significant decrease in peak left ventricular pressure and LV dp/dt, but LVEDP and left ventricular end-diastolic circumference did not change. Thus, during ischemia there was no alteration of the pressure-volume relationship. Furthermore, the pressure-volume relationship did not change during restoration of flow.

These results do not necessarily imply the absence of subtle changes in left ventricular wall thickness or shape; they do indicate, however, that there was no overall distortion of the relationship of external circumference to internal volume. As illustrated in the lower-left of each of the two bottom right panels of figure 5, at very low end-diastolic pressures the pressure-circumference curve was, on occasion, steep. Relatively small changes in circumference occurred with substantial changes in end-diastolic pressure. At these very low end-diastolic pressures this may reflect the fact that the initial circumferential changes were not detected at a time when the heart wall was "snagging up" against the mercury-in-silastic gauges. Thus, it is possible in these isolated instances that this may reflect variations in the prestretch applied to the gauges. This effect, however, does not invalidate the observations made at higher pressures and circumferences.

Recent studies have demonstrated that cell swelling may occur during myocardial ischemia and be exacerbated when flow is restored (Powell, unpublished data). In view of this, it seemed possible that repetitve ischemia and reflow might alter the pressure-volume relationship even though initial ischemia and reflow had not. However, two of the present experiments designed to evaluate this possibility demonstrated that two successive periods of ischemia, each followed by a period of restoration of flow, did not affect the pressure-volume relationship.

It seems evident from the results that the elevation of left ventricular end-diastolic pressure in the globally ischemic, otherwise normal, canine myocardium is due to a decrease in the overall systolic performance of the heart rather than to alterations in the pressure-volume relationship of the left ventricle. It must be emphasized that the present study is one of acute global ischemia of normal canine myocardium, a condition which differs from coronary artery disease in man, in which there may be local areas of fibrosis and local areas of myocardial ischemia. It is also possible that segmental, severe, acute ischemia in man may be more severe than that produced in the present global ischemia model. Thus, it is possible that, under these circumstances, a decrease in compliance might occur in severely ischemic myocardial segments in man.

Another fundamental difference between the model employed in the present study and ischemia in man is that in the present study the pericardium was open and the influence of right ventricular filling pressures on the pressure-volume characteristics of the left ventricle was minimized. It is possible that those who have observed a shift in the pressure-volume curve in man during acute ischemia are correct but that the changes observed do not reflect changes of muscle stiffness but rather the effects of external mechanical constraints upon left ventricular filling which were minimized in the present study.

Thus, it is important to exercise caution in extrapolating the results of this study to patients with coronary artery disease. There is agreement that patients with chronic coronary artery disease complicated by past myocardial infarctions may develop a shift of the left ventricular pressure-volume relationship in the direction of increased ventricular stiffness, in the resting state. There is less agreement as to whether an acute alteration of diastolic pressure-volume relationships occurs during clinical angina. Possible reasons for the conflicting results of these studies during angina would seem to fall into two general categories.
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First, there are potential methodological problems in left ventricular volume determination. In a study of McLaurin et al.,4 where echocardiographic end-diastolic internal diameter was utilized as an index of volume, it was concluded that there was an apparent decrease in left ventricular diastolic compliance during pacing-induced angina. The authors note, however, that “the echocardiographic technique samples only a small portion of the left ventricle and changes in ventricular geometry or the symmetry of contraction may be missed.” This limitation might account for the conflicting results obtained by O’Brien et al.3 in that study, O’Brien reported no diastolic pressure volume alterations during acute ischemia utilizing echocardiographic volume determinations. Similarly, it is not certain whether difficulties with angiographic determinations of volume might not account for discrepancies between the results of Dwyer,1 Barry et al.,4 and Sharma et al.7 These studies involve left ventriculography before and during induced angina. The angiographic technique of volume determination assumes that the left ventricle is an ellipsoid of revolution — an assumption which conceivably could be invalid during regional ischemia. In addition, the studies of Dwyer and Barry et al. assume that left ventricular volume may be calculated from single plane ventriculograms, both at rest and during ischemia. The latter investigation of nine patients with coronary artery disease reported that both an increase in ventricular stiffness and a fall in contractility may occur during angina. Five of the patients had a fall in ejection fraction of substantial degree without a significant rise in angiographic end-diastolic volume, implying a fall in stroke volume. Yet, indicator dilution cardiac outputs also done during angina did not show a fall in stroke volume in three of these patients. If the reported ejection fraction changes are assumed to be correct and the change in end-diastolic volume is calculated from the indicator dilution stroke volume, substantial rises in end-diastolic volume accompany the increases in end-diastolic pressure in eight of the nine patients.

Secondly, it is possible that several pathophysiological events occur in angina, and that these events may vary in magnitude among patients. For example, the patient studied by Dwyer who had the largest rise in end-diastolic pressure during angina also had a large rise in end-diastolic volume and fall in ejection fraction (acute fall in left ventricular systolic performance). The result of angina in this patient was similar to that found by Sharma et al.7 in 12 patients, where large rises in end-diastolic pressure and end-diastolic volume and a fall in ejection fraction occurred. On the other hand, four other patients investigated by Dwyer developed what appeared to be an acute fall in left ventricular compliance during angina, although there was little change in end-diastolic pressure. These patients may be similar to those studied by echocardiographic techniques in the report of McLaurin et al.

The results of the human studies cited indicate that the mechanism of end-diastolic pressure rises in patients with acute ischemia is yet to be established definitely. The present study shows that in the acutely ischemic, but otherwise normal, ventricle the rise in end-diastolic pressure is not due to a shift in pressure-volume relationships, but is secondary to a decrease in left ventricular contractility.

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References


Appendix

All ischemic left ventricular end-diastolic pressure-circumference relationships were statistically compared with the pressure-circumference relationship obtained in the nonischemic control period. The comparison was based upon the demonstrated exponential relationship between pressure and volume in the arrested left ventricle.19 The same relationship was assumed to hold at end-diastole, thus

\[ P(V) = a_1 + a_2 e^{V/V_0} \]

where \( P \) is end-diastolic pressure as a function of end-diastolic volume, \( V \); \( a_1 \), \( a_2 \), and \( V_0 \) are constants for a given ventricle under given fixed conditions. End-diastolic volumes are not directly available, so the above relationship 1) is adapted to apply to volume ratios:

\[ P(V/V_0) = a_3 + a_4 e^{V/V_0} \]

where \( a_3 = a_1 V_0 \). The constants \( a_3 \) are to be obtained from a least-squares fit to the data. The requisite volume ratios were obtained using an ellipsoid model of fixed eccentricity of the heart. Then one can write:

\[ V = S'V_0 \text{ or } V/V_0 = S' \]

where \( S' \) represents a length scaling factor along the three geometrical axes.
For the baseline volume, $V_b$, the relationship between left ventricular volume and circumference is

$$V_b = qC_b^3$$

where $q$ is a shape factor related to the (arbitrary) shape of the end-diastolic left ventricle (e.g., for a sphere $q = \frac{4}{3\pi}$). The model also assumes that at end-diastole the wall thickness is a small fraction of the mean ventricular radius; then,

$$V = qC^3 = qSC_b^3$$

so that, using 3) and 4)

$$\frac{V}{V_b} = S = \left(\frac{C}{C_b}\right)^3$$

and from 2) and 6)

$$P(C) = a_1 + a_2 C^{a_3C_b^3}$$

Using a Davidson-Fletcher-Powell nonlinear function minimization algorithm, the function 7) is fit to the observed control pressure-volume relationships. The output of this computer subprogram is a set of estimates of the three parameters $a_1$, $a_2$, and $a_3$. Using these parameters to 7), the analysis program computes the predicted pressure at each actually observed circumference, using the minimum cubed circumference observed in the control period as $C_b$, the baseline circumference. The squared difference between this predicted pressure and the end-diastolic pressure actually observed gives an estimate of the variance of the observed pressures about the predicted pressure-volume curve, when summed over all points observed in the control period. A similar procedure gives the estimated variance about the same predicted pressure-volume curve in each ischemic period. The ratio of the estimated ischemic variance about the predicted pressure-volume curve to the control variance about the same curve yields the statistic $F^{10}$ which is used to test the hypothesis that the ischemic pressure-volume observations come from the same underlying pressure-circumference curve as the control period observations. In all cases, the computed $F$ was consistent with the hypothesis ($P > 0.01$, single-tailed test) that the observations made during ischemia were samples from the same pressure-volume curve as that generated from the control observations. Thus, it can be inferred that ischemia does not alter any of the parameters $(a_1$, $a_2$, $a_3)$ which characterize the predicted pressure-volume relationship. Consequently, the parameters characterizing the pressure-volume relationship $(a_1$, $a_2$, $a_3)$ must remain unaltered by ischemia. Since left ventricular end-diastolic volume stiffness is determined by these parameters, it is concluded that end-diastolic volume stiffness is unaltered by ischemia.

Heart Rate and Arterial Blood Pressure during Exercice in Patients with Angina Pectoris

Effects of Training and of Nitroglycerin

JAN PRAETORIUS CLAUSEN, M.D., AND JENS TRAP JENSEN, M.D.

SUMMARY In 29 patients with typical exertional angina pectoris, intra-arterial systolic blood pressure (SBP), heart rate (HR), and the rate-pressure product (RPP = HR × SBP × 10−2) were continuously recorded during repeated bouts of leg or arm exercise. Development of chest pain was independent of the workload and occurred at a fairly constant value of RPP, of HR, and of SBP in each patient for a given type of exercise, but the pain threshold values for all three variables were consistently higher during arm exercise than during leg exercise. The reproducibility of the pain threshold values was assessed for leg exercise. The variation, based on individual coefficients of variation, ranged from 1.3% to 13% (group mean, about 6%). There was no significant difference between the SBP values obtained by the traditional, noninvasive cuff technique and the values during intra-arterial monitoring.

In 25 patients a physical training program of an average of three months increased the maximal amount of work (watt × sec) performed before onset of pain by 100%. The most conspicuous effect of training on cardiac function was a 10% reduction of HR at a given workload, SBP being unchanged. Over-all, the data suggest that the increased exercise capacity caused by training could be accounted for by the reduction in the relation between RPP and external workload. The improvement in exercise capacity resulting from training was on the same level of magnitude as the 90% increase obtained in 11 untrained patients after administration of 0.25 to 0.50 mg of nitroglycerin sublingually prior to exercise. In contrast to the finding after training, nitroglycerin administered to subjects increased HR by 10%, but reduced SBP by 13%, RPP remaining unchanged. Therefore to explain the effect of nitroglycerin on exercise capacity additional economizing changes in myocardial performance (e.g., reduction of heart volume) are required.

It is well documented that most patients with angina pectoris on exertion develop an increased exercise capacity from a period of physical training. After training the patients are able to exercise for longer time at a given workload or sustain a higher workload before pain develops. The main reason for the increased exercise capacity is assumed to be a reduced myocardial oxygen consumption (MVO2) at a given total body oxygen consumption (VO2). In patients with coronary artery disease, as well as in young healthy subjects, MVO2 can be estimated from the heart rate (HR) and the systolic blood pressure (SBP) or the product of these variables — the so-called rate-pressure product (RPP). Accordingly, anginal pain — which is supposed to reflect an insufficient myocardial oxygen supply in relation to the oxygen requirements — occurs at a fairly constant RPP threshold value in the individual patient both when provoked by exercise and when provoked by other situations which increase HR and SBP. Physical training reduces HR and often also SBP at a given VO2 and thus in the trained state longer time and/or higher workloads can be reached before the critical RPP threshold value at which pain is elicited occurs. In addition a higher
Left ventricular end-diastolic pressure volume relationships with experimental acute global ischemia.
I Palacios, R A Johnson, J B Newell and W J Powell, Jr

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