# Hyperkinesis without the Frank-Starling mechanism in a nonischemic region of acutely ischemic excised canine heart

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ABSTRACT To determine the essential mechanism of increased systolic wall motion, i.e., hyperkinesis, in a nonischemic region (NIR) during acute ischemia, we simultaneously evaluated global and regional function of the excised, cross-circulated canine left ventricle connected to a volume servo pump before and after coronary occlusion. Regional areas were determined with pairs of orthogonal subendocardial sonomicrometers in the ischemic region (IR) and NIR. After coronary occlusion with left ventricular end-diastolic and stroke volumes kept constant, the amount of systolic area shrinkage ($\Delta A$) in NIR increased by $33 \pm 41\%$ ($p < .05$), despite a decrease in end-diastolic regional area by $3 \pm 4\%$ ($p < .05$). Regional work obtained from the wall tension–regional area (T-A) loop in NIR decreased by $50 \pm 24\%$ due to a similar decrease in afterload despite the presence of hyperkinesis, indicating regional systolic unloading. When left ventricular end-diastolic volume was subsequently increased with a constant stroke volume, $\Delta A$ in NIR increased at the expense of a further decrease in $\Delta A$ in IR. The end-systolic T-A relationship in NIR remained unchanged, whereas that in IR markedly shifted rightward, suggesting that the contractile state of NIR was constant. These results indicate that hyperkinesis in NIR during acute ischemia can occur without a utilization of the Frank-Starling mechanism or an enhancement of regional contractile state, and that the essential mechanism of this phenomenon is regional afterload reduction due to an intraventricular mechanical interaction between IR and NIR.
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AN INCREASE in systolic wall motion, i.e., hyperkinesis, in a nonischemic region of the left ventricle during acute ischemia has been shown in experimental animals[1–10] and in patients[11–13] by assessment of systolic segment shortening or wall thickening. Three possible mechanisms responsible for this phenomenon have been proposed from the results of studies in hearts in situ: increased sympathetic stimulation,[1, 6, 12] a utilization of the Frank-Starling mechanism,[4, 8] and a mechanical interaction between ischemic and nonischemic regions.[9, 14, 15]

Nakano[1] first described an increase in contractile force in a nonischemic region and related it to increased sympathetic activity. Theroux et al.[4] demonstrated increased systolic segment shortening in a nonischemic region that correlated well with an increase in end-diastolic segment length and interpreted the increased shortening as a manifestation of a compensatory operation of the Frank-Starling mechanism. Thereafter, an increase in systolic segment shortening or wall thickening in a nonischemic region has been shown by many others[5–8, 11] and has been ascribed to either compensatory operation of the Frank-Starling mechanism or increased sympathetic activity. More recent studies by Lew et al.[9, 14] and Smalling et al.[15] have attributed the increased segment shortening to a combination of the Frank-Starling mechanism and mechanical unloading due to an intraventricular interaction between the ischemic and nonischemic regions.

However, all these studies were performed in hearts in situ in which acute ischemia is usually accompanied by compensatory operation of the Frank-Starling mechanism and myocardial function is regulated by various neurohumoral mechanisms. This has made it difficult to separate the effects of the Frank-Starling mechanism and neurohumoral factors from other

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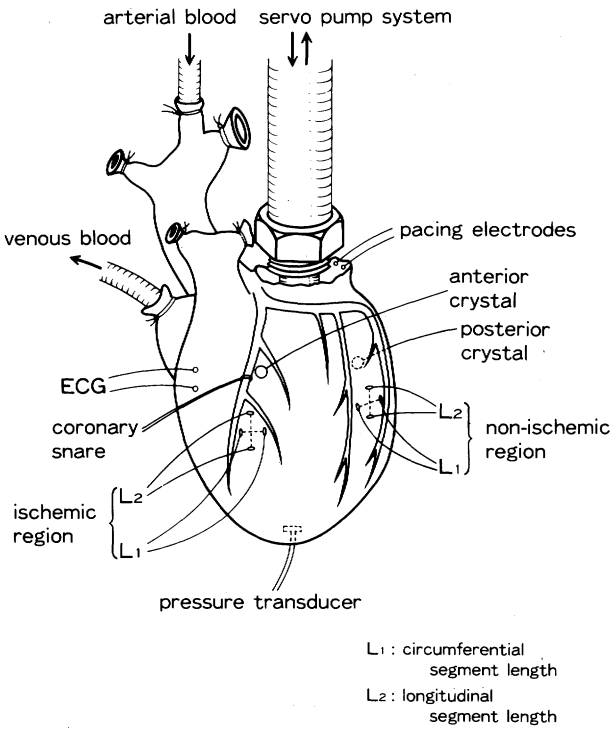


**FIGURE 1.** Schematic drawing of heart preparation. The isolated heart was perfused by arterial blood from a support dog to which coronary venous blood was returned. A volume servo pump system, connected to a left ventricular (LV) balloon, controlled and measured LV volume using the epicardial ECG for a trigger. Anterior and posterior ultrasonic crystals measured LV short-axis diameter. Two pairs of orthogonal segment lengths were measured with pairs of ultrasonic crystals placed on the anterior and posterior wall regions, one of which was rendered ischemic with a snare placed on the coronary artery.

mechanism(s) that might be responsible for the hyperkinesis. Accordingly, this study was undertaken in excised, volume-controlled hearts to clarify the essential mechanism(s) of hyperkinesis in the nonischemic region of the acutely ischemic heart, with special attention to whether hyperkinesis can occur in the nonischemic region without utilization of the Frank-Starling mechanism, and whether the contractile state of the region is enhanced during hyperkinesis.

## Methods

**Heart preparation.** Experiments were performed on the left ventricles of 12 isolated canine hearts. In each experiment, two mongrel dogs (body weight 13 to 22 kg) were anesthetized with ketamine hydrochloride (5 to 7 mg/kg im) followed by intravenous $\alpha$-chloralose (45 mg/kg) and urethane (450 mg/kg). The heart donor dog was thoracotomized under artificial ventilation. The left subclavian artery and the right ventricle of the donor dog were cannulated and connected to the common carotid arteries and the external jugular vein of the support dog, respectively, with cross-circulation tubes (figure 1). The heart was isolated from pulmonary and systemic circulations and was excised from the chest.

The left atrium was opened and the left ventricular chordae tendineae were cut. A thin rubber balloon with an unstretched volume of 60 ml tied on a balloon-to-pump connecter was fitted in the left ventricle, and its mouth was secured at the mitral anulus. Left ventricular pressure was measured with a miniature pressure gauge (Konigsberg, P-7) placed inside the apical end of the balloon. The balloon was connected to the same volume servo pump described previously.[16, 17] With this volume servo pump, we were able to precisely control and accurately measure instantaneous left ventricular volume.

The arterial blood pressure of the support dog served as the coronary perfusion pressure of the excised heart. The mean level of this pressure in all 12 experiments averaged 90 ± 19 (SD) mm Hg during the control measurement, and was relatively constant throughout each experiment. The support dog was ventilated with room air, and supplemental oxygen and intravenous sodium bicarbonate were given when necessary to maintain arterial pH, $Po_2$, and $Pco_2$ within their physiologic ranges.

The temperature of the heart was maintained within 35° to 37° C with a heater placed on the cross-circulation tubes. A pair of pacing electrodes was placed on the left atrial appendage. A ventricular epicardial electrocardiogram (ECG) was recorded with another pair of electrodes to trigger the volume servo pump and to determine the onset of contraction.

**Placement of ultrasonic crystals.** Left ventricular short-axis diameter was measured with a pair of crystals (5 MHz, 2.5 mm in diameter) placed on the endocardial surface of the ventricular wall adjacent to the anterior and posterior descending coronary arteries (figure 1). These two crystals were on the equatorial plane perpendicular to the basal-to-apical long axis. Two pairs of orthogonal segment lengths, one in the left ventricular anterior wall region and the other in the posterior wall region, were measured with pairs of ultrasonic crystals (2 mm in diameter) implanted in the left ventricular subendocardium. The anterior and posterior wall crystals were placed completely within the perfusion area of the left anterior descending and circumflex coronary arteries, respectively. The first pair of crystals in each region was placed in the equatorial circumference, and the

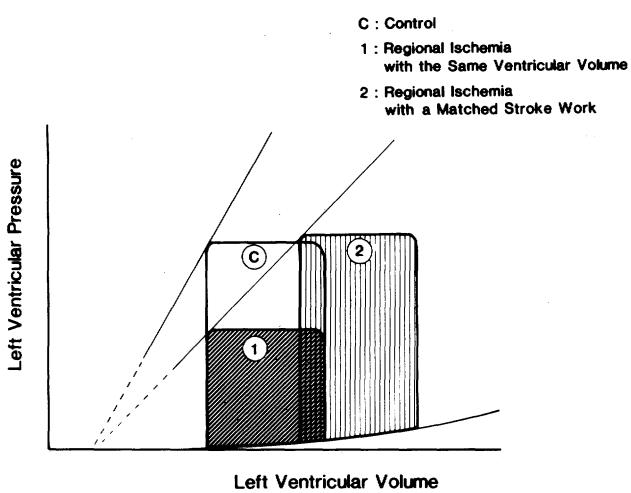


**FIGURE 2.** Schematic illustration of experimental protocol in the left ventricular (LV) pressure-volume diagram. After the control measurement, regional ischemia was produced by coronary occlusion with LV end-diastolic and stroke volumes kept constant (stage 1 of regional ischemia). LV end-diastolic volume was then increased with stroke volume kept constant to a volume at which LV systolic pressure and LV stroke work regained their control values (stage 2 of regional ischemia). The end-systolic pressure-volume relationship passing through the left upper corners of the pressure-volume loops during regional ischemia indicates that LV contractile state is lower during regional ischemia than during the control period, but remains constant throughout stages 1 and 2 of regional ischemia.

second pair was placed in the longitudinal direction, perpendicular to the first pair. Both segments were 1 to 2 cm in length, crossing each other at their respective midpoints. The subendocardial position of each ultrasonic crystal was verified at postmortem examination. Each pair of crystals was connected to an ultrasonic dimension system (NEC San-Ei, model 4105).[18]

**Experimental protocol.** In control contractile state, left ventricular end-diastolic and stroke volumes were arbitrarily set with the volume servo pump at 22.6 ± 2.2 ml (range 19.8 to 26.3 ml) and 6.3 ± 0.6 ml (5.2 to 7.7 ml), respectively. With these left ventricular volumes, left ventricular end-diastolic and end-systolic pressures averaged 9.5 ± 4.3 mm Hg (1.5 to 17.3 mm Hg) and 94 ± 15 mm Hg (69 to 122 mm Hg), respectively. In steady-state contractions with a set of left ventricular end-diastolic and stroke volumes, the ECG, left ventricular pressure, volume, and dimensions for short-axis diameter, and orthogonal segment lengths in both anterior and posterior regions were measured. After the control measurements, the left anterior (nine experiments) or circumflex (three experiments) coronary artery was occluded with a snare to produce regional ischemia, with left ventricular end-diastolic and stroke volumes kept constant with the volume servo pump. Hereafter, an observed region that was perfused with the occluded coronary artery was called an ischemic region, and the other, a nonischemic region. Fifteen minutes were allowed to elapse until a new steady state was reached, and measurements with the same left ventricular volumes as the control were made during regional ischemia. This was called stage 1 of regional ischemia (figure 2), in which the compensatory Frank-Starling mechanism was not allowed to operate. Next, left ventricular end-diastolic volume was increased with the volume servo pump to a volume at which left ventricular end-systolic pressure, and hence left ventricular stroke work, regained their control values with stroke volume kept constant. Measurements were then repeated during steady-state contractions. This was called stage 2 of regional ischemia (figure 2). Heart rate was kept constant by atrial pacing throughout the measurements in seven experiments and was not paced in five experiments.

**Data analysis.** All data were recorded on a multichannel thermal pen recorder and processed with a signal processor (NEC San-Ei, 7T17 with Signal Basic No. 5). The input signals were digitized at a sampling interval of 2 msec, on-line processed, and stored in a floppy disk. End-diastole was determined at the onset of QRS wave of epicardial ECG. End systole was defined as the time when the ratio $P(t)/[V(t)-V_0]$ became maximal, where P(t) and V(t) are left ventricular instantaneous pressure and volume and $V_0$ is the ventricular volume at which peak isovolumetric pressure is zero.[19] To assess left ventricular global function, a left ventricular pressure-volume loop during one cardiac cycle was constructed and left ventricular stroke work was calculated as the integral of left ventricular pressure with respect to the volume from one end-diastole to the next. The level of ventricular contractile state was determined in terms of an index of ventricular contractile state, Emax, as the maximal or end-systolic value for the ratio $P(t)/[V(t)-V_0]$.[19]

To assess regional contractile performance in the ischemic and nonischemic regions, wall tension–regional area (T-A) loops in the ischemic and nonischemic regions (figure 3) were constructed based on reported theoretical and experimental studies.[16, 20–22] Wall tension of the left ventricle was calculated according to the force equilibrium relationship[23] of a thick-walled sphere, assuming that the left ventricular contractile force is supported solely by the endocardial layer.[20] Namely, T = ¼ D P, where T is wall tension (mm Hg·cm, or dyne/cm), D is left ventricular short-axis diameter (cm), and P is left ventricular pressure (mm Hg). Wall tension is also called surface or hoop tension.[23] Dimensions of wall tension (mm Hg·cm) indicate

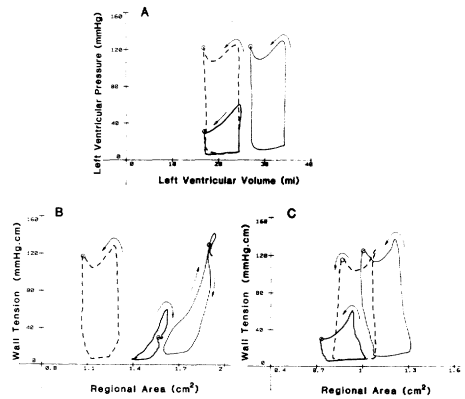


**FIGURE 3.** A representative example of left ventricular (LV) pressure-volume loops (*A*) and T-A loops in ischemic (*B*) and nonischemic (*C*) regions during the control period (dashed line) and stage 1 (thick solid line) and stage 2 of regional ischemia (thin solid line). During the control period, all pressure-volume and T-A loops rotated counterclockwise and were rectangular. During stage 1 of regional ischemia, however, the T-A loop in the ischemic region rotated clockwise, and showed a significant area expansion during the isovolumetric contraction period and area shrinkage during the isovolumetric relaxation period. Note that the area shrinkage during the isovolumetric contraction period in the nonischemic region corresponds to the isovolumetric area expansion in the ischemic region. During stage 2 of regional ischemia, when LV end-diastolic volume was increased with a constant stroke volume, LV systolic pressure and stroke work regained their control values. However, reciprocal area expansion and shrinkage during isovolumetric periods were still observed in both regions.

force per unit circumferential length because 1 mm Hg·cm = $1.33 \times 10^3$ dyne/cm. Regional area was calculated as $A = \frac{1}{2} L_1 L_2$, where A is regional area ($cm^2$), and $L_1$ and $L_2$ are circumferential and longitudinal segment lengths (cm). Regional work of both ischemic and nonischemic regions was assessed from the integral of wall tension T with respect to the regional area A of each region from one end-diastole to the next. This integral yielded the area within a T-A loop.[16, 21] The T-A loop method has been validated in our previous studies[16, 22] and reliably measures left ventricular regional work with physically correct dimensions (mm Hg·ml or dyne·cm) in both normal and regionally ischemic hearts.

Systolic area shrinkage in each region was assessed as the end-diastolic regional area minus the end-systolic regional area. We chose area shrinkage rather than segment shortening as an index to assess multidirectional shortening of a ventricular region because segment shortening reflects only unidirectional behavior of the region[16, 24] and hence is easily affected by myocardial fiber orientation.[25, 26] Therefore, systolic segment shortening in the circumferential and longitudinal directions, calculated as the end-diastolic segment length minus the end-systolic segment length, were used only as supplemental data. Area shrinkages during isovolumetric contraction and ejection periods were determined as the end-diastolic regional area minus the area at the time of peak left ventricular wall tension and the area at the time of peak wall tension minus the end-systolic regional area, respectively, because left ventricular wall tension was considered to be maximal at the onset of ejection when the pressure-volume loop was rectangular, as in this study (figure 3).

Finally, to assess changes in contractile state in each region, we analyzed the end-systolic T-A relationship during the control and regional ischemia periods. Because Emax values during the two stages (stage 1, 4.7 ± 1.5 mm Hg/ml; stage 2, 5.3 ± 1.5 mm Hg/ml) were not significantly different, the global contractile

state of the left ventricle was considered to be unchanged during these two stages of regional ischemia. Therefore, we connected the two end-systolic T-A data points obtained during stages 1 and 2 of regional ischemia, and compared the relative position of the end-systolic T-A relationship during regional ischemia to the one end-systolic T-A data point during the control period.

**Statistics.** Statistical comparisons of data obtained during control, stage 1 of regional ischemia, and stage 2 of regional ischemia were performed by two-way analysis of variance.[27] When analysis of variance indicated a significant difference among the three conditions, a paired t test with Bonferroni's correction[27] was performed to determine the significance of difference between conditions. Specifically, a significance level of $.05/3 = .017$ was chosen in conducting each of the three individual comparisons, so that the p value would be smaller than .05 for the set. Data are presented as the mean ± SD unless otherwise indicated.

## Results

Figure 3 shows a representative example of left ventricular pressure-volume loops and T-A loops in ischemic and nonischemic regions obtained during the control period and at stages 1 and 2 of regional ischemia. During the control period, all of the pressure-volume and T-A loops were rectangular, i.e., there was almost no increase (expansion) or decrease (shrinkage) in regional area during the isovolumetric contraction and relaxation periods in either the ischemic or nonischemic region. In addition, all loops rotated counterclockwise, so that left ventricular stroke work and regional work in both regions were positive.

During stage 1 of regional ischemia (thick solid line), left ventricular systolic pressure and wall tension decreased, while left ventricular end-diastolic and stroke volumes were kept constant. End-diastolic regional area in the ischemic region increased despite the same left ventricular end-diastolic pressure (figure 3, *B*), suggesting creep or passive stretch of the ischemic myocardium. The T-A loop in this region showed a significant area expansion and shrinkage during the isovolumetric contraction and relaxation periods, respectively, i.e., systolic stretch and early diastolic shortening. As a result, systolic area shrinkage in this region markedly decreased from 0.17 $cm^2$ during control to $-0.15$ $cm^2$ during stage 1 of regional ischemia. In addition, the rotation of the T-A loop in the ischemic region reversed to the clockwise direction, and thus regional work of this region decreased markedly from 24.0 to $-3.0$ mm Hg·ml.

In the nonischemic region (figure 3, *C*), end-diastolic regional area decreased slightly as a reciprocal change to the increase in end-diastolic area in the ischemic region, i.e., preload did not increase in this ventricular region as well as at the level of the whole ventricle. The T-A loop in this region showed a significant area shrinkage during the isovolumetric contraction period and area expansion during the isovolumetric relaxation periods. Note that this behavior corresponded reciprocally to those during isovolumetric periods in the ischemic region. As a result, systolic area shrinkage in this region increased from 0.20 $cm^2$ during control to 0.28 $cm^2$ during stage 1 of regional ischemia, despite the apparent lack of utilization of the Frank-Starling mechanism. Interestingly, regional work of this region decreased considerably from 24.4 to 8.2 mm Hg·ml, despite the presence of significant hyperkinesis.

During stage 2 of regional ischemia (thin solid line), when left ventricular end-diastolic volume was increased with a constant stroke volume, left ventricular systolic pressure regained the level during the control state. End-diastolic regional area and end-systolic wall tension in both ischemic and nonischemic regions increased concomitantly. As a result, regional work of the ischemic region decreased further to $-11.0$ mm Hg·ml, whereas that of the nonischemic region increased to 27.8 mm Hg·ml and exceeded the control value. In spite of these changes in preload, afterload, and regional work, area expansion during the isovolumetric contraction period and area shrinkage during the isovolumetric relaxation period in the ischemic region, as well as the reciprocal behavior in the nonischemic region, remained significant. In this stage of regional ischemia, systolic area shrinkage in the ischemic region further decreased to $-0.30$ $cm^2$ and that in the nonischemic region further increased to 0.31 $cm^2$, despite the constant left ventricular stroke volume.

Similar qualitative changes in T-A loops in the ischemic and nonischemic regions were observed in each of the other 11 experiments. Heart rate was not significantly different among the three conditions (control 136 ± 15 beats/min, stage 1 of regional ischemia 136 ± 15 beats/min, and stage 2 of regional ischemia 139 ± 16 beats/min).

Table 1 summarizes left ventricular global function data during the control period, stage 1 of regional ischemia, and stage 2 of regional ischemia. During stage 1 of regional ischemia, Emax, an index of left ventricular contractile state, decreased by 54.2 ± 17.0% from the control value, whereas left ventricular end-diastolic pressure, end-diastolic volume, and stroke volume were not different from those during the control period. Left ventricular end-systolic pressure and stroke work decreased by 53.6 ± 17.2% and 51.8 ± 17.7%, respectively. Peak and end-systolic wall tensions also decreased by 47.3 ± 15.9% and 54.6 ± 17.4% due to the decrease in left ventricular systolic pressure. During stage 2 of regional ischemia,

**TABLE 1**
**Variables of left ventricular global function**

| | Control | Regional ischemia | |
|---|---|---|---|
| | | Stage 1 | Stage 2 |
| Emax (mm Hg/ml) | 10.8 ± 3.2 | 4.7 ± 1.5[B] | 5.3 ± 1.5[B] |
| LVEDP (mm Hg) | 9.5 ± 4.3 | 9.0 ± 4.4 | 17.9 ± 8.7[B,C] |
| LVESP (mm Hg) | 94.3 ± 14.9 | 42.5 ± 13.2[B] | 94.8 ± 16.6[C] |
| LVEDV (ml) | 22.6 ± 2.2 | 22.6 ± 2.2 | 31.8 ± 4.1[B,C] |
| SV (ml) | 6.3 ± 0.6 | 6.3 ± 0.6 | 6.3 ± 0.5 |
| LVSW (mm Hg·ml) | 531.9 ± 122.2 | 247.2 ± 72.3[B] | 525.4 ± 127.7[C] |
| Peak T (mm Hg·cm) | 66.5 ± 22.0 | 34.4 ± 12.4[B] | 76.4 ± 24.7[B,C] |
| EST (mm Hg·cm) | 58.1 ± 21.2 | 25.2 ± 8.7[B] | 66.4 ± 24.0[A,C] |

Values are mean ± SD.

LVEDP = left ventricular end-diastolic pressure; LVESP = left ventricular end-systolic pressure; LVEDV = left ventricular end-diastolic volume; SV = stroke volume; LVSW = left ventricular stroke work; T = left ventricular wall tension; EST = end-systolic wall tension.

[A]$p < .05$; [B]$p < .01$ compared with each control value; [C]$p < .01$ compared with values of stage 1.

when left ventricular end-diastolic volume was increased with a constant stroke volume, left ventricular end-systolic pressure and stroke work regained their respective control levels. Peak and end-systolic wall tensions exceeded the respective control values because left ventricular volume was larger than the control value.

Left ventricular regional function data during the control period and stages 1 and 2 of regional ischemia are shown in table 2 and figures 4 and 5. During stage 1 of regional ischemia, end-diastolic regional area in the ischemic region significantly increased by 7.3 ± 8.9%, whereas that in the nonischemic region significantly decreased by 3.1 ± 3.7%. End-diastolic length of the circumferential and longitudinal segments also increased in the ischemic region and decreased in the nonischemic region, although these changes were not statistically significant. Systolic area shrinkage in the ischemic region markedly decreased by 108.6 ± 30.2%, and systolic segment shortening also decreased, indicating akinesis or dyskinesis due to regional ischemia. In contrast, systolic shortening of the circumferential segment and systolic area shrinkage in the nonischemic region significantly increased by 35.2 ± 42.0% and 32.7 ± 40.9%, respectively, despite the absence of an increase in preload and a constant stroke volume; i.e., hyperkinesis occurred without utilizing the Frank-Starling mechanism (figure 4). The decrease in systolic area shrinkage in the ischemic region was attributable mainly to area expansion during the isovolumetric contraction period, and the increase in systolic area shrinkage in the nonischemic region was attributable, in turn, to the reciprocal area shrinkage during the same period (table 2).

Regional work of the ischemic region obtained from the T-A loop markedly decreased by 98.7 ± 18.3% (8.7 ± 5.9 to 0.2 ± 1.5 mm Hg·ml) during stage 1 of regional ischemia (figure 5). Regional work of the nonischemic region during this stage also significantly decreased by 49.8 ± 24.3% (10.8 ± 3.2 to 4.7 ± 1.5

**TABLE 2**
**Variables of left ventricular regional function**

| | Ischemic region | | | Nonischemic region | | |
|---|---|---|---|---|---|---|
| | | Regional ischemia | | | Regional ischemia | |
| | Control | Stage 1 | Stage 2 | Control | Stage 1 | Stage 2 |
| Circumferential segment | | | | | | |
| EDL (cm) | 1.43 ± 0.26 | 1.48 ± 0.28 | 1.66 ± 0.30[B,D] | 1.39 ± 0.27 | 1.37 ± 0.29 | 1.52 ± 0.29[B,D] |
| ΔL (cm) | 0.17 ± 0.09 | 0.00 ± 0.07[B] | −0.05 ± 0.07[B,C] | 0.16 ± 0.08 | 0.19 ± 0.05[A] | 0.22 ± 0.06[B,D] |
| Longitudinal segment | | | | | | |
| EDL (cm) | 1.58 ± 0.22 | 1.63 ± 0.21 | 1.68 ± 0.26[A,C] | 1.63 ± 0.27 | 1.61 ± 0.26 | 1.67 ± 0.28[A,D] |
| ΔL (cm) | 0.06 ± 0.12 | −0.01 ± 0.08[A] | −0.09 ± 0.07[B] | 0.05 ± 0.07 | 0.07 ± 0.08 | 0.05 ± 0.07 |
| Regional area | | | | | | |
| EDA ($cm^2$) | 1.13 ± 0.24 | 1.20 ± 0.23[A] | 1.40 ± 0.31[B,D] | 1.15 ± 0.35 | 1.12 ± 0.35[A] | 1.29 ± 0.38[B,D] |
| ΔA ($cm^2$) | 0.18 ± 0.08 | −0.01 ± 0.06[B] | −0.13 ± 0.11[B,C] | 0.15 ± 0.05 | 0.19 ± 0.06[A] | 0.22 ± 0.05[B,D] |
| $\Delta A_{iso}$ ($cm^2$) | 0.08 ± 0.08 | −0.07 ± 0.06[B] | −0.17 ± 0.13[B] | 0.00 ± 0.08 | 0.05 ± 0.07[B] | 0.05 ± 0.07[B] |
| $\Delta A_{ej}$ ($cm^2$) | 0.10 ± 0.05 | 0.06 ± 0.03 | 0.05 ± 0.04 | 0.15 ± 0.05 | 0.14 ± 0.06 | 0.16 ± 0.06 |

Values are mean ± SD.

EDL = end-diastolic segment length; ΔL = amount of systolic segment shortening; EDA = end-diastolic regional area; ΔA = amount of systolic area shrinkage; $\Delta A_{iso}$ = area shrinkage during the isovolumetric contraction period; $\Delta A_{ej}$ = area shrinkage during the ejection period.

[A]$p < .05$, [B]$p < .01$ compared with each control value; [C]$p < .05$, [D]$p < .01$ compared with values of stage 1.

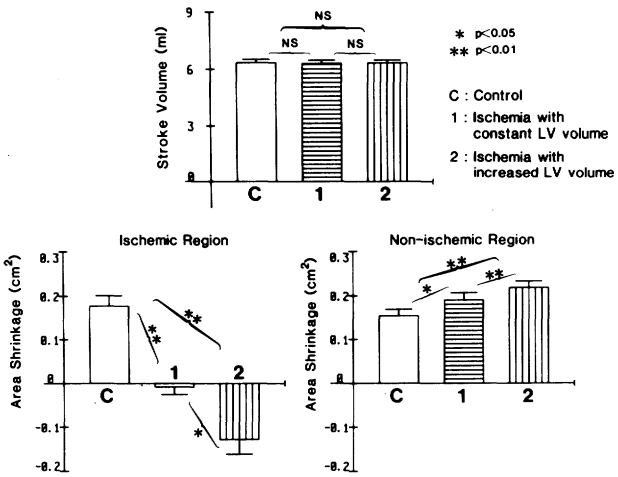


**FIGURE 4.** Comparisons of stroke volume (*top*) and systolic area shrinkage in the ischemic (*bottom left*) and nonischemic (*bottom right*) regions during the control period and stages 1 and 2 of regional ischemia. Means ± SE are indicated.

mm Hg·ml), despite the presence of hyperkinesis in this region, because peak and end-systolic wall tensions decreased due to the decrease in left ventricular systolic pressure.

During stage 2 of regional ischemia, end-diastolic segment lengths and regional areas in both regions significantly increased from the corresponding stage 1 values because of the increase in left ventricular end-diastolic volume (table 2). Systolic shortening of the circumferential segment and systolic area shrinkage in the ischemic region decreased further to negative values ($-47.8 \pm 73.6\%$ and $-85.3 \pm 60.8\%$ of the respective control values), whereas those in the nonischemic region increased further to $159.9 \pm 56.4\%$ and $153.6 \pm 47.8\%$ of the respective control values, despite the constant stroke volume (figure 4). Regional work of the ischemic region also decreased further to a negative value ($-1.7 \pm 3.1$ mm Hg·ml) (figure 5), indicating that work was performed on the ischemic region by the surrounding nonischemic myocardium. In contrast, regional work of the nonischemic region significantly increased to $14.4 \pm 6.3$ mm Hg·ml, exceeding the control value by $30.6 \pm 28.2\%$ despite the same left ventricular stroke work as at control.

Figure 6 shows the end-systolic T-A relationships during the control and regional ischemia periods in the ischemic and nonischemic regions. Because the control T-A relationship consisted of a single data point, we assessed only the relative position rather than the slope of the two relationships. During regional ischemia, the end-systolic T-A relationship in the ischemic region shifted markedly to the right of the control point, whereas that in the nonischemic region remained almost unchanged from the control data point.

## Discussion

In the present study we have shown that hyperkinesis in the nonischemic region of an acutely ischemic heart can occur without utilization of the Frank-Starling mechanism. We made five major observations that point to the essential mechanism of hyperkinesis in the nonischemic region: (1) a significant increase in systolic area shrinkage in the nonischemic region without an increase in preload of the region, but with a significant decrease in afterload, (2) a further increase in systolic area shrinkage in the nonischemic region at the expense of a further decrease in systolic area shrinkage in the ischemic region when left ventricular end-diastolic volume was increased with a constant stroke volume, (3) a significant decrease in regional work of the nonischemic region despite the presence of hyperkinesis, (4) an almost constant end-systolic T-A relationship in the nonischemic region throughout the control and regional ischemic periods, and (5) demonstration of hyperkinesis in an excised heart preparation that is free of systemic neurohumoral influence. These findings indicate that the essential mechanism for hyperkinesis in the nonischemic region during acute ischemia is regional afterload reduction due to an intraventricular mechanical interaction between the ischemic and nonischemic regions, rather than compensatory operation of the Frank-Starling mechanism or increased sympathetic activity.

The first observation was that hyperkinesis occurred

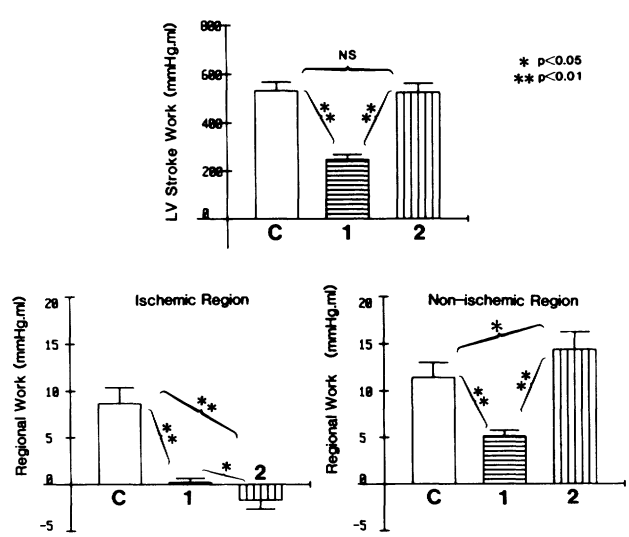


**FIGURE 5.** Comparisons of left ventricular stroke work (*top*) and regional work in the ischemic (*bottom left*) and nonischemic (*bottom right*) regions during the control period (C) and stages 1 and 2 of regional ischemia. Means ± SE are indicated.

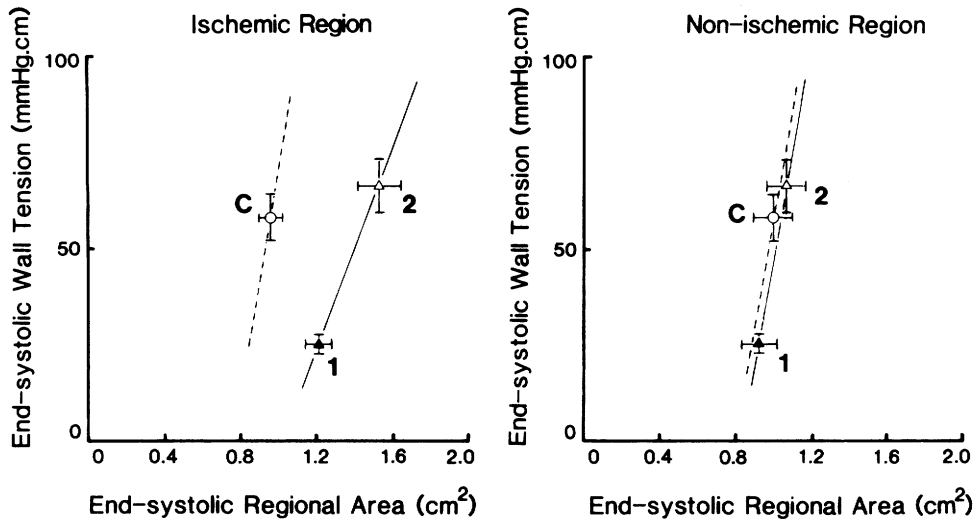


**FIGURE 6.** The end-systolic T-A relationship in the ischemic (*left*) and nonischemic (*right*) regions during the control period (open circle) and regional ischemia (closed triangle for stage 1 and open triangle for stage 2). The solid line was drawn by connecting the two end-systolic T-A data points during regional ischemia. The dashed line is an assumed line indicating the end-systolic T-A relationship during the control period. Note that the end-systolic T-A relationship in the ischemic region shifted markedly to the right after coronary occlusion, whereas the relationship in the nonischemic region remained almost constant. Means ± SE are indicated.

in the nonischemic region during stage 1 of regional ischemia even when left ventricular end-diastolic and stroke volumes were kept constant. The increase in systolic area shrinkage in the nonischemic region was accompanied by a reciprocal decrease in area shrinkage in the ischemic region. This finding indicates that the Frank-Starling mechanism is not an essential mechanism for the hyperkinesis and suggests an intraventricular mechanical interaction between the ischemic and nonischemic regions as the responsible mechanism.

The second observation was that systolic area shrinkage in the nonischemic region increased further during stage 2 of regional ischemia when left ventricular end-diastolic volume was increased with a constant stroke volume. This is of interest because in a normal heart without intraventricular regional interaction, an

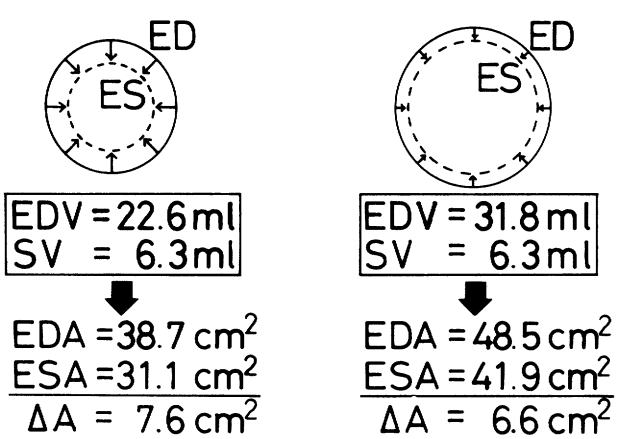


**FIGURE 7.** Calculation of total systolic area shrinkage of the left ventricular endocardial surface in a spherical model without intraventricular regional interaction. With end-diastolic volume (EDV) of 22.6 ml and stroke volume (SV) of 6.3 ml, as in stage 1 of the present study (*left*), total end-diastolic area (EDA) is calculated as 38.7 $cm^2$, total end-systolic area (ESA) as 31.1 $cm^2$, and total systolic area shrinkage (ΔA) as 7.6 $cm^2$. When EDV is increased to 31.8 ml with a constant SV of 6.3 ml, as in stage 2 of the present study (*right*), total ΔA is calculated as 6.6 $cm^2$, which is 13% smaller than the initial ΔA. ED = end-diastole; ES = end-systole.

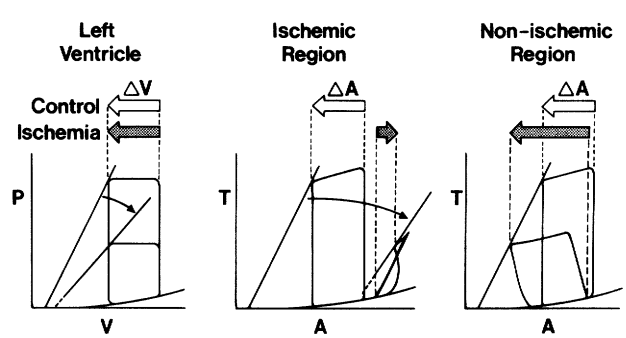


**FIGURE 8.** Schematic illustration for explanation of the mechanism of hyperkinesis without utilization of the Frank-Starling mechanism. Left ventricular pressure-volume (P-V) loops (*left*) and T-A loops in the ischemic (*middle*) and nonischemic (*right*) regions during control and regional ischemia periods are shown. End-diastolic and stroke volumes are constant under both conditions. Open and shaded arrows indicate stroke volume (ΔV) and the amount of systolic area shrinkage (ΔA) during the control period (open arrows) and regional ischemia (shaded arrows). The lines passing through the left upper corners of the loops indicate end-systolic P-V or T-A relationships. During regional ischemia, ΔA in the ischemic region becomes negative (systolic bulge) with a marked rightward shift of the end-systolic T-A relationship, whereas ΔA in the nonischemic region increases (hyperkinesis) without any increase in preload or enhancement of contractile state of the region. See text for more discussion.

increase in end-diastolic volume with a constant stroke volume inevitably results in a decrease in systolic area shrinkage. For example, according to a spherical model in which left ventricular volume (V) and endocardial surface area (A) are given as $V = (4/3)\pi r^3$ and $A = 4\pi r^2$, where r is the radius of the sphere, an end-diastolic volume of 22.6 ml and stroke volume of 6.3 ml as the average values in stage 1 of the present study yield a total endocardial systolic area shrinkage of 7.6 $cm^2$ (figure 7). When this end-diastolic volume is increased to 31.8 ml with a constant stroke volume as in stage 2, the total endocardial systolic area shrinkage is calculated as 6.6 $cm^2$, which is 13% smaller than that during stage 1. If we use total systolic shortening around the circumference of the sphere instead of total endocardial systolic area shrinkage in this model, it also decreases by 23% from 1.14 cm during stage 1 to 0.88 cm during stage 2. When these results are taken into account, the observed increase in systolic area shrinkage in the nonischemic region during stage 2 is a large change. Because this hyperkinesis was again accompanied by a reciprocal decrease in systolic area shrinkage in the ischemic region, the phenomenon of intraventricular mechanical interaction between the ischemic and nonischemic regions was clearly demonstrated.

The third observation was that regional work of the nonischemic region obtained from the T-A loop area decreased during stage 1 of regional ischemia despite the significant hyperkinesis. This reduction of regional work was attributable to the decrease in left ventricular systolic pressure and systolic wall tension (i.e., reduction of afterload) with constant left ventricular end-diastolic and stroke volumes rather than a decreased contractile state of the region. Similar findings (increased segment shortening and decreased segmental work index) have been reported by Sasayama et al.[13] using cineangiography in patients with coronary artery disease, although the dimensions of their segmental work index (mm·mm Hg or dyne/cm) are different from the physical dimensions of work (mm Hg·ml or dyne·cm) and left ventricular volume was not controlled. The reduction of regional work of the nonischemic region suggests that hyperkinesis is not a "compensatory" mechanism for the decreased contractile performance of the ischemic region, but a natural consequence of mechanical unloading of the nonischemic region. This situation is analogous to an unloaded whole ventricle in which a decrease in arterial pressure (afterload) results in an increase in stroke volume (shortening) and a decrease in stroke work.[28] Thus, hyperkinesis in the nonischemic region does not always indicate "hyperfunction" in terms of work performance.

The fourth observation was that the end-systolic T-A relationship in the nonischemic region remained almost unchanged throughout the control and regional ischemia periods despite the evolving hyperkinesis, whereas this relationship in the ischemic region shifted markedly to the right of control. Because the end-systolic T-A relationship is practically linear and shifts leftward during global enhancement of contractile state with dobutamine and rightward during global ischemia with a lower perfusion pressure,[16, 22, 29] this relationship may reflect regional contractile state independent of both preload and afterload, by the analogy of the end-systolic pressure-volume relationship in the whole ventricle.[19] The shift of this relationship in the present study, therefore, seems to indicate that the contractile state of the nonischemic region remained almost constant, whereas that of the ischemic region was markedly depressed during regional ischemia. This is evidence that hyperkinesis is not caused by an enhanced contractile state of the nonischemic region due to increased sympathetic stimulation.

The fifth observation was that hyperkinesis was demonstrated in an excised heart that was independent of a reflex increase in sympathetic nerve discharge or circulating catecholamines after coronary occlusion. Although an excised, cross-circulated heart could be influenced by circulating catecholamines from the support dog, blood pressure and heart rate of the support dog remained unchanged after coronary occlusion of the excised heart in the present study, indicating constant sympathetic activity of the support dog. Pashkow et al.[6] considered reflex sympathetic activity to be responsible for the increased contractile force in the nonischemic region, because an increase in contractile force was abolished after transection and cannulation of the proximal circumflex coronary artery and its perivascular neural fibers. However, their result might have been affected by the brief period of ischemia in the "nonischemic" region during the cannulation procedure, which was performed between the control and postcannulation measurements. Thus, our demonstration of hyperkinesis in an excised heart indicates that an increased sympathetic activity is not a primary mechanism for hyperkinesis in the nonischemic region.

Our hypothetical explanation of the mechanism of hyperkinesis without utilization of the Frank-Starling mechanism is illustrated in figure 8. During the control period, both the ischemic and nonischemic regions are able to generate and support wall tension, resulting in neither area shrinkage nor expansion during isovolumetric contraction and relaxation periods. During regional ischemia with constant left ventricular end-diastolic and stroke volumes, the end-systolic T-A

relationship in the ischemic region shifts markedly to the right, whereas that in the nonischemic region remains constant because the contractile state of the nonischemic region remains unchanged. Because of depressed contractile function, the ischemic region is no longer able to support the wall tension that is generated by the nonischemic myocardium during the isovolumetric contraction period.[3] This results in area expansion of the ischemic region and hence reciprocal area shrinkage of the nonischemic region during the isovolumetric contraction period (intraventricular regional interaction). Since the ischemic region is unable to generate an adequate amount of tension until end-systole, systolic wall tension of the left ventricle (which acts as afterload on the nonischemic region) decreases, allowing the nonischemic region to shorten to a greater extent without any increase in preload. This decrease in systolic wall tension also results in a decrease in regional work of the nonischemic region, defined as the area within the T-A loop. Thus, intraventricular afterload reduction in the nonischemic region results in both hyperkinesis without utilization of the Frank-Starling mechanism and a decrease in regional work of the region due to a decrease in systolic wall tension. If preload is allowed to increase, however, regional work will increase due to an increase in systolic wall tension, as in stage 2 of the present study.

We prefer the T-A loop method to the conventional pressure-length loop method for three major reasons. First, the pressure-length loop method can provide only unidirectional assessment of regional function, whereas myocardial fibers are variously oriented within the left ventricle[30] and the extent and time course of segment shortening are different depending on the orientation of the segment.[16, 24–26] Second, the dimensions of the pressure-length loop area (mm Hg·cm or dyne/cm) differ from those of work or energy (dyne·cm or joule).[16, 21] In contrast, the T-A loop area (mm Hg·ml) has the same dimensions as work or energy because 1 mm Hg·ml = $1.33 \times 10^{-4}$ J. Third, we cannot directly compare two pressure-length loop areas from different-sized hearts, since force acting on the two wall segments is different because of the different radii even when left ventricular pressure and segment length are the same. Thus, the conventional pressure-length loop method cannot be used to assess regional work in a physically sound manner.

One potential source of error in our assessment of regional work by the T-A loop method is related to the calculation of wall tension based on the force-equilibrium relationship for a spherical model. Our use of short-axis diameter as the diameter of the sphere might result in a small underestimation of regional work.[16] In addition, in a regionally ischemic heart, changes in regional radius of curvature, which were not measured in the present study, would occur in the ischemic region, and hence might affect wall tension of this region.[31] However, our previous study[22] has shown that the global integral of regional work determined by the T-A loop method closely agrees with measured total left ventricular work both before and after coronary occlusion, suggesting that the influence of changes in regional wall tension on the measurement of regional work during regional ischemia is very small.

An increase in preload has been reported to reduce the mechanical disadvantage imposed by the ischemic or weak myocardium, leading to an increase in total effective shortening and hence forward stroke volume,[14] because the steep portion of the passive pressure-length relationship may limit the excessive lengthening during the isovolumetric contraction period of the ischemic myocardium.[14, 32] However, in the present study, an increase in left ventricular end-diastolic volume resulted in further decreases in systolic area shrinkage and regional work in the ischemic region. This suggests that the ischemic region does not always behave as a completely passive material. In other words, the extent and severity of ischemia, and hence the amount of inhomogeneously distributed viable tissue within the ischemic region, may be more dynamically varied by changes in ventricular loading conditions than previously thought.

There seems to be some disagreement among investigators as to whether hyperkinesis is an isovolumetric or ejection phase phenomenon.[2, 9, 10, 14, 15] Although our results are compatible with previous studies of Sedek and Lewartowski[2] and Lew et al.,[9, 14] i.e., the increase in segment shortening in the nonischemic region occurred during the preejection (isovolumetric) period, Smalling et al.[15] and Akaishi et al.[10] have reported a significant increase in segment shortening during the ejection period and no increase during the preejection period. Type of preparation (isolated heart in the present study, open-chest dog,[2, 9, 10, 14] and "chronically" instrumented closed-chest dog[15]) and duration of coronary occlusion (15 sec,[15] 2 min,[2] 3 min,[9] 15 min in the present study, 30 min,[14] and graded coronary stenosis[10]) vary among the studies. In addition, the timing of end-ejection of the heart in situ differs from that of end-systole defined in the present study.[33] These factors may account for the discrepancy of results between the studies.

Although it is difficult to directly apply our results obtained in excised and volume-controlled hearts to a

clinical setting in which compensatory responses such as the Frank-Starling mechanism or increased sympathetic stimulation can be used, some points of interest should be discussed. In patients with acute myocardial infarction, left ventricular end-diastolic volume usually increases, whereas stroke volume remains constant or decreases because end-systolic volume also increases due to a depressed left ventricular contractile state.[11] In some patients, hyperkinesis in the nonischemic region may be observed.[11, 12] This situation is very similar to stage 2 of regional ischemia in the present study. Under this condition, nothing but intraventricular interaction between ischemic and nonischemic regions can explain the hyperkinesis because, without regional interaction, an increase in end-diastolic volume with a constant or decreased stroke volume inevitably results in a virtual decrease in systolic area shrinkage or segment shortening, as discussed above (figure 7). Even an enhancement of contractile state of the nonischemic region due to increased sympathetic activity cannot increase segmental shortening with a constant or decreased stroke volume unless ischemic and nonischemic regions interact with each other. Thus, even in the clinical setting, regional afterload reduction due to an intraventricular mechanical interaction between ischemic and nonischemic regions rather than the Frank-Starling mechanism should be the primary mechanism for hyperkinesis in the nonischemic region.

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## References


1. Nakano J: Effect of changes in coronary arterial blood flow on the myocardial contractile force. Jpn Heart J **7:** 78, 1966
2. Sedek G, Lewartowski B: Mechanism of changes in left ventricular function after acute experimental coronary occlusion. Cardiovasc Res **7:** 313, 1973
3. Lewartowski B, Sedek G: Mechanical performance of the left ventricle at early stages of experimental ischemia. Mechanism of shortening of ejection period. Cardiovasc Res **8:** 593, 1974
4. Theroux P, Franklin D, Ross J Jr, Kemper WS: Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. Circ Res **35:** 896, 1974
5. Theroux P, Ross J Jr, Franklin D, Kemper WS, Sasayama S: Regional myocardial function in the conscious dog during acute coronary occlusion and responses to morphine, propranolol, nitroglycerin, and lidocaine. Circulation **53:** 302, 1976
6. Pashkow F, Holland R, Brooks H: Early changes in contractility and coronary blood flow in the normal areas of the ischemic porcine heart. Am Heart J **93:** 349, 1977
7. Nakamura M, Sasayama S, Takahashi M, Ohyagi A, Yamamoto A, Lee J, Kawai C: Regional dysfunction of the interventricular septum during acute coronary artery occlusion. Cardiovasc Res **16:** 144, 1982
8. Molaug M, Geiran O, Kiil F: Compensatory cardiac mechanisms evoked by septal ischemia in dogs. Am J Cardiol **51:** 201, 1983
9. Lew WYW, Chen Z, Guth B, Covell JW: Mechanisms of augmented segment shortening in nonischemic areas during acute ischemia of the canine left ventricle. Circ Res **56:** 351, 1985
10. Akaishi M, Schneider RM, Mercier RJ, Agarwal JB, Helfant RH, Weintraub WS: Analysis of phases of contraction during graded acute myocardial ischemia. Am J Physiol **250:** H778, 1986
11. Rigaud M, Rocha P, Boschat J, Farcot JC, Bardet J, Bourdarias JP: Regional left ventricular function assessed by contrast angiography in acute myocardial infarction. Circulation **60:** 130, 1979
12. Sheehan FH, Mathey DG, Schofer J, Krebber H, Dodge HT: Effect of interventions in salvaging left ventricular function in acute myocardial infarction: a study of intracoronary streptokinase. Am J Cardiol **52:** 431, 1983
13. Sasayama S, Nonogi H, Fujita M, Sakurai T, Wakabayashi A, Kawai C, Eiho S, Kuwahara M: Analysis of asynchronous wall motion by regional pressure-length loops in patients with coronary artery disease. J Am Coll Cardiol **4:** 259, 1984
14. Lew WYW, Ban-Hayashi E: Mechanisms of improving regional and global ventricular function by preload alterations during acute ischemia in the canine left ventricle. Circulation **72:** 1125, 1985
15. Smalling RW, Ekas RD, Felli PR, Binion L, Desmond J: Reciprocal functional interaction of adjacent myocardial segments during regional ischemia: An intraventricular loading phenomenon affecting apparent regional contractile function in the intact heart. J Am Coll Cardiol **7:** 1335, 1986
16. Goto Y, Suga H, Yamada O, Igarashi Y, Saito M, Hiramori K: Left ventricular regional work from wall tension-area loop in canine heart. Am J Physiol **250:** H151, 1986
17. Suga H, Hisano R, Hirata S, Hayashi T, Yamada O, Ninomiya I: Heart rate–independent energetics and systolic pressure-volume area in dog heart. Am J Physiol **244:** H206, 1983
18. Goto Y, Yamamoto J, Saito M, Haze K, Sumiyoshi T, Fukami K, Hiramori K: Effects of right ventricular ischemia on left ventricular geometry and end-diastolic pressure-volume relationship in the dog. Circulation **72:** 1104, 1985
19. Suga H, Sagawa K, Shoukas AA: Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res **32:** 314, 1973
20. Suga H, Goto Y, Yamada O, Igarashi Y: Is regional ventricular wall work determined from regional force and shortening always consistent with the law of conservation of energy? Jpn Circ J **48:** 1007, 1984
21. Sugawara M, Tamiya K, Nakano K: Regional work of the ventricle: Wall tension-area relation. Heart Vessels **1:** 133, 1985
22. Goto Y, Hiramori K, Suga H: Quantitative evaluation of left ventricular regional work from wall tension-regional area loop in canine heart. Jpn Circ J **51:** 114, 1987
23. Fung YC: Biomechanics. Mechanical properties of living tissues. New York, 1981, Springer-Verlag
24. Lew WYW, LeWinter MM: Regional comparison of midwall segment and area shortening in the canine left ventricle. Circ Res **58:** 678, 1986
25. Gallagher KP, Osakada G, Hess OM, Koziol JA, Kemper WS, Ross J Jr: Subepicardial segmental function during coronary stenosis and the role of myocardial fiber orientation. Circ Res **50:** 352, 1982
26. Freeman GL, LeWinter MM, Engler RL, Covell JW: Relationship between myocardial fiber direction and segment shortening in the midwall of the canine left ventricle. Circ Res **56:** 31, 1985
27. Snedecor GW, Cochran WG: Statistical methods, ed 7. Ames, IA, 1980, Iowa State University Press
28. Sagawa K: Analysis of the ventricular pumping capacity as a function of input and output pressure loads. *In* Reeve EB, Guyton AC, editors: Physical bases of circulatory transport: regulation and exchange. Philadelphia, 1967, Saunders, ch 9, pp 141–149
29. Goto Y, Yamada O, Igarashi Y, Suga H, Hiramori K, Saito M, Haze K, Sumiyoshi T, Fukami K: Different effects of global and regional ischemia on left ventricular regional function. An analysis by wall tension-area relation. Jpn Circ J **49:** 863, 1985 (abst)
30. Streeter DD Jr, Spotnitz HM, Patel DP, Ross J Jr, Sonnenblick EH: Fiber orientation in the canine left ventricle during diastole and systole. Circ Res **24:** 339, 1969
31. Janz RF: Estimation of local myocardial stress. Am J Physiol **242:** H875, 1982
32. Akaishi M, Weintraub WS, Schneider RM, Klein LW, Agarwal JB, Helfant RH: Analysis of systolic bulging. Mechanical characteristics of acutely ischemic myocardium in the conscious dog. Circ Res **58:** 209, 1986
33. Sagawa K: The end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use. Circulation **63:** 1223, 1981