Observations on Factors Affecting Local Forces in the Left Ventricular Wall during Acute Myocardial Ischemia

By Heinrich R. Schelbert, James W. Covell, John W. Burns, Peter R. Maroko, and John Ross, Jr.

ABSTRACT

The factors affecting local myocardial function in the presence of ischemic myocardial damage may considerably influence cardiac function and the extent of tissue damage resulting from the initial ischemic injury. However, previous attempts to study local wall forces in the ischemic myocardium have produced variable results. In the present study, a technique was developed for recording isometric left ventricular wall tension that minimized artifacts due to external forces acting on the ischemic area. Miniature isometric force gauges were implanted in 23 dogs in the left ventricular wall within a zone buffered by two rows of transmural prongs attached to a ring. During a test occlusion of a branch of the left anterior descending coronary artery, the ischemic area was defined by the presence of epicardial ST segment elevation, and force gauges were implanted in marginal or ischemic areas of the myocardium. During a subsequent coronary occlusion wall force in the ischemic area fell immediately by an average of $31 \pm 8\%$. When the occlusion was repeated during isoproterenol infusion, wall tension decreased in previously unaffected areas of the myocardium, although in ischemic areas it remained above previous control ischemic levels. Arterial counterpulsation improved the development of wall tension in the ischemic area by $27\%$ and decreased the extent and amount of ST segment elevation. Thus the present study clearly indicates a significant reduction but not elimination of active myocardial wall force in ischemic zones following experimental coronary occlusion. Moreover, force could be augmented by either isoproterenol or counterpulsation, and counterpulsation can produce a significant improvement in function of the ischemic myocardium while reducing the area of ischemic injury.

KEY WORDS ischemic counterpulsation left ventricular wall force isometric force gauge myocardial infarction coronary occlusion

Many therapeutic procedures have been utilized in the treatment of acute myocardial infarction but little is known about the influence of these procedures on local function of ischemic myocardium and myocardium adjacent to the area of ischemic injury. It is well known that hemodynamic factors can influence local isometric force recorded in the left ventricle (1, 2), and recently Newman and Walton (3) suggested that both bulging of the myocardium and the indirect effect of the surrounding normal tissue on the gauge can importantly affect the measurement of force within an ischemic area of the myocardium. As a result of these difficulties, the effect of coronary occlusion per se on local wall forces is not clear, both increases and decreases in local wall force having been reported (2-8). In the present study, a "buffering" row of pins was placed in the myocardium around the force gauge to minimize the effects of the surrounding myocardium. With this approach, local iso-
ISCHEMIA AND VENTRICULAR WALL FORCE

metric force development could be measured in the normal and ischemic myocardium following an acute coronary occlusion. In addition, the influences of isoproterenol and counterpulsation on local force development prior to and during coronary occlusion were examined.

Methods

Experiments were performed on 23 dogs weighing 17–30 kg and anesthetized with pentobarbital sodium (30 mg/kg). A bilateral thoracotomy was performed and ventilation was maintained with a Harvard respiratory pump. Left ventricular (LV) and aortic pressures were monitored through wide-bore stainless steel cannulas inserted into the apex of the left ventricle and the left subclavian artery, respectively, and attached directly to Statham model P23Db transducers.

Recently it has been shown that acute ST segment alterations in the epicardial surface electrocardiogram correlate well with the extent of myocardial ischemic injury measured by the fall in myocardial creatine phosphokinase activity 24 hours after experimental coronary occlusion (9). These studies also demonstrated that reproducible maps can be obtained serially in the same animal when occlusions are shorter than 15 minutes. Accordingly, an ST segment map was first made to define the area of myocardial injury produced by occlusion (with a Schwartz intracranial arterial clamp) of the left anterior descending coronary artery, the left circumflex coronary artery or one or more branches of these vessels (9). After 10 minutes the initial occlusion was then released. Isometric wall force was monitored with miniature isometric force transducers which, except for a 50% reduction in size (8 X 13 mm), were similar in design to that described by Feigl (10). However, to obtain appropriate sensitivity the flexure plates were replaced by 0.006-inch stainless steel, and the strain gauges were reduced in size (BLH no. SR4-FAB06G12S6). These modified gauges showed a linear relationship between voltage output and force applied over the range of forces measured. Moreover, harmonic analysis of a pulsed change in force revealed a flat frequency response to 30 Hz. These miniaturized isometric force transducers were then inserted into one of three sites of the left ventricular myocardium, defined by previous ST segment map:

1. In an ischemic area: epicardial ST segment elevation of greater than 2 mv on all four sides of the implanted gauge.
2. In a marginal area: ST segment elevation on one or two contiguous sides of the gauge.
3. In normal myocardium: no ST segment elevation around the gauge.

Previous studies using isometric force gauges in acutely ischemic myocardium have shown an increase, a decrease, or no change in force in the ischemic zone (2–8), suggesting that forces exerted on the gauge and ischemic myocardium by muscle not subtended by the gauge importantly influence measured force. Accordingly, preliminary experiments were carried out to examine the influence of alterations in overall ventricular performance on the isometric force recordings. In three animals the isometric force gauge alone was implanted in the myocardium. As observed previously by Newman and Walton (4), when slits were placed almost through the left ventricular wall at both ends of the force gauge (parallel to the recording pins) there was an increase in recorded myocardial wall force.

![FIGURE 1](image)

Schematic drawing of the preparation and the assembled isometric force gauge. FG = isometric force gauge shown in cross-section encircled by the buffer device; LV = left ventricle; RV = right ventricle; LCC = left circumflex coronary artery; LAD = left anterior descending coronary artery; SG = strain gauge. The open circles represent the sampling sites for epicardial electrocardiograms.
experiments confirmed that forces external to the
gauge influenced the level of measured force
development. In all additional experiments, a
buffering row of pins was placed around the
gauge. The buffering row of pins was placed on a
rectangular frame (10 × 20 mm) which was first
implanted into the left ventricular wall; the
isometric gauge was then inserted inside the
buffer ring (Fig. 1). The gauge was initially
implanted with the pins 8 mm apart. In all
experiments, after insertion of the buffering pins,
the distance between the pins was increased until
active force was maximal. The average extension
of the gauge was 30% ± 1% (SE). Under these
conditions in four experiments, when a slit was
placed distal to the buffering row of pins and
parallel to the recording pins, no augmentation
of force was observed. The results of these experi-
ments and those of Newman and Walton (4)
indicate that with the buffering row of pins in
place, factors tending to decrease the force
determined by the gauge are minimized and the
only external forces not attenuated by the buffer
are those tending to increase force. In acute
coronary occlusion, it might be expected that two
important factors could influence measured local
force; (1) impaired function of the isometric
segment of muscle subtended by the gauge and
(2) increase in force development by the
remainder of the heart due to compensating
augmentation of left ventricular end-diastolic
volume and muscle length. Since, without the
buffer, both of these factors would tend to
diminish measured force, it seemed of critical
importance to ensure that any observed change in
force was due to impaired function of the
subtended segment only. Accordingly, in all
experiments, buffering pins were placed outside
the force gauge.

To determine that alterations in left ventricular
pressure and left ventricular end-diastolic volume
alone had little influence on the recording of
isometric wall force, a brief episode of partial
ascending aortic obstruction was produced in
each experiment prior to coronary ligation and
again just prior to release of the occlusion. Peak
left ventricular pressure was increased by an
average of 42 mm Hg (101–143 mm Hg).
However, these large increases in pressure
produced only an average of 12% augmentation of
peak wall force. Moreover, these changes in force
were linearly related to the pressure change, and
these induced changes in peak left ventricular
pressure were always much larger than those
observed during coronary occlusion (Table 1).

At the end of the experiment, left ventricular
wall thickness at the gauge was measured and in
all except five experiments the gauge was then
calibrated by applying weights to the pins and
the recorded force expressed as force per unit
area (stress) assuming the pins subtended all the
force applied to this area.

In six animals the initial coronary occlusion was
released, and 30 minutes after return to the
control hemodynamic conditions, an isoproterenol
infusion (0.06–0.47 µg kg⁻¹ min⁻¹) was initiated.
The occlusion was then repeated 5 minutes after
the response to isoproterenol had stabilized. In 11
experiments the occlusion of the coronary artery
was maintained and either counterpulsation (7
experiments) or isoproterenol infusion (4
experiments) was initiated and maintained for 5–15
minutes.

Counterpulsation was achieved using a servo-
controlled pump system (11). The withdrawal
phase of the pump cycle was initiated from the R-
wave of the electrocardiogram.

In seven experiments counterpulsation was
initiated 5 minutes prior to occlusions and
maintained throughout the duration of the
occlusion. In four of the seven experiments the
effects of counterpulsation were examined during
occlusion and arterial hypotension
produced by exsanguination. The statistical
significance of results were determined using a t-
test for paired samples (12).

Results

Effects of acute coronary occlusion

The effects of acute coronary occlusion are
shown in Table 1, and representative record-
nings are shown in Figure 2. Following
coronary occlusion, average left ventricular
end-diastolic pressure increased slightly (by
0.5 mm Hg), and the overall hemodynamic
changes were minimal and statistically insig-
nificant. The average control isometric ven-
tricular wall stress was 380.7 ± 19.9 (SE) g/cm².
Following coronary occlusion, isomet-
ric wall stress was not altered in areas where
no epicardial ST segment change occurred
(Table 1, col. NF). In both the marginal and
ischemic areas of the myocardium, wall stress
fell significantly by an average of 22.2% (Table
1, cols. MF and IF) (P < 0.01). However, in the
marginal area the average decrease in force
was less than in the ischemic area,
averaging 18.7% and 31.4% respectively, and
the greatest decrease in force occurred in an
ischemic area (68%). Moreover, marginal area
force was not always depressed and did not
decrease in 2 of the 19 experiments (3 of the
21 marginal gauges).
Table 1: Effects of Coronary Ligation on Local Myocardial Wall Stress

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<th>LVEDP</th>
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<td>Occ</td>
<td>C</td>
<td>Occ</td>
<td>C</td>
<td>% change</td>
</tr>
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<td>150</td>
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</table>

Abbreviations: C = control; Occ = during coronary occlusion; LVP = left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; wall stress (g/cm²): in "normal" myocardium, NF; in "marginal" myocardium, MF; in "ischemic" myocardium, IF (see text); % change = change from control level before coronary occlusion.
POSTEXTRASYSTOLIC POTENTIATION AND MECHANICAL ALTERNANS IN ISCHEMIC TISSUE

The response of gauges implanted in ischemic and marginal tissue to spontaneous extrasystoles was markedly different. Moreover, spontaneously occurring mechanical alternans within the ischemic and marginal myocardium was frequently observed. In gauges within the marginal myocardium, alternans was observed in 6 of 21 (29%) of the coronary occlusions, and the incidence was similar in gauges within the ischemic myocardium (2 of 7). As shown in Figure 3, 5 of 7 gauges in ischemic areas lacked normal postextrasystolic augmentation, whereas only 2 of the 21 gauges in marginal tissue did so.

EFFECTS OF ISOPROTERENOL

Following a control ligation and release of the occlusion, isoproterenol (avg. 0.135 µg kg⁻¹ min⁻¹) was administered in seven experiments in seven animals (Table 2 and Fig. 2). All force gauges were implanted in marginal areas. Heart rate was increased from control levels of 149 ± 10 to an average of 192 ± 9 beats/min (Table 2) and isometric force was significantly augmented to 171% ± 30% of control levels (P < 0.01) (Table 2, C2, Iso). The fall in force occurring with the initial occlusion averaged 21.6 ± 8% (P < 0.01). The fall in force following occlusion during isoproterenol infusion was similar (26.6 ± 5%). However, the absolute decrease in wall force was 2.1 times greater during isoproterenol infusion. Despite this larger fall, force development during occlusion and isoproterenol infusion (18.4±1.9 units) remained above control ischemic levels (9.8 ± 1.6 units). Moreover, in one experiment in gauges in which no fall occurred during the control occlusion (Table 2, expt 8, both gauges), a decrease in stress was observed following isoproterenol infusion and coronary occlusion, indicating that under appropriate circumstances, isoproterenol can augment the myocardial injury to such an extent that it depresses function over a wider area. This extension of the area of depressed function was directly related to an extension of the area of marked ST segment elevation. Thus the number of sites showing significant ST segment elevation during the control occlusion was increased from 6.4 ± 1.9 to 7.2 ± 0.6, and these results are similar to those observed previously (9).

When isoproterenol was administered following coronary occlusion in four additional animals, isometric stress in the ischemic area could still be augmented (194 g/cm² control, 305 g/cm² isoproterenol).

In both the maintained and intermittent occlusion studies, there was an augmentation of the average epicardial ST segment elevation following isoproterenol infusion (0.75 ± 1.2 mv control compared to 5.4 ± 1.1 mv following isoproterenol).

EFFECTS OF ARTERIAL COUNTERPULSATION

The effects of arterial counterpulsation were examined in seven experiments during a maintained coronary occlusion in five animals (Table 3, Fig. 4). Three of the studies were performed in "normotensive" animals (Table 3; peak LV pressure greater than 80) and the
### TABLE 2

**Effects of Isoproterenol on Wall Force during Ischemia**

<table>
<thead>
<tr>
<th>Expt</th>
<th>HR</th>
<th>Isoproterenol (µg kg⁻¹ min⁻¹)</th>
<th>Isom force (units)</th>
<th>ST (mV)</th>
<th>Avg ST (mV)</th>
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</thead>
<tbody>
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</tr>
<tr>
<td></td>
<td>Occ</td>
<td>183</td>
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<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>C 2</td>
<td>183</td>
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<td></td>
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<tr>
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<td>Iso</td>
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<td>12.4</td>
<td>1</td>
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<td>174</td>
<td>18.5</td>
<td>20</td>
<td>6.6</td>
</tr>
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</table>

**Force Gauge 1**

| C 1  | 183 | 13.3 | 0 | 0.2 |
| Occ  | 150 | 14.0 | 3 | 1.0 |
| C 2  | 150 | 11.4 |  |    |
| Iso  | 150 | 20.1 | 0 | 0.1 |
| Iso + occ | 185 | 15.4 | 7 | 3.4 |

**Force Gauge 2**

| C 1  | 150 | 15.8 | 0 |    |
| Occ  | 150 | 16.7 | 3 |    |
| C 2  | 150 | 10.4 |  |    |
| Iso  | 150 | 21.4 |  |    |
| Iso + occ | 19.9 | 19.9 | 12 |    |

C 1 and Occ = control and during initial coronary occlusion; C 2 = steady state after release of occlusion and recovery; Iso = during isoproterenol infusion; Iso + Occ = occlusion during isoproterenol infusion; Isom force = isometric force in recorder divisions (uncalibrated gauges); ST = ST segment elevation from a representative epicardial site near the force gauge; Avg ST = average ST segment elevation from all sites.

remaining four in "hypotensive" animals (peak LV pressure 43 to 77 mm Hg, Table 3). In all animals, counterpulsation produced an average decrease in left ventricular end-diastolic pressure during infarction from 8.7 ± 1.2 to 6.9 ± 0.85 mm Hg, while aortic mid-diastolic pressure was significantly increased from 80 ± 12 to 101 ± 10 mm Hg (Table 3). All gauges were in marginal tissue and following occlusion stress fell significantly (from control levels of 308 ± 7 g/cm² to 206 ± 22 g/cm²; P < .05). Following counterpulsation, isometric force increased slowly and stabilized at 242 ± 24 g/cm² (P < .01 compared to the level before counterpulsation). Moreover, this augmentation of wall...
stress was maintained 10 minutes after counterpulsation was stopped (avg. 224 ± 24 g/cm²; P < .01 compared to the level during occlusion but before counterpulsation).

These effects were more pronounced in the four studies in which the animal was hypertensive (Fig. 4). Counterpulsation produced a larger average increase in local stress development (19.6% compared to 11.1% in the normotensive animals). Moreover, this augmentation of local wall stress was frequently accompanied by an increase in peak left ventricular pressure and mean arterial pressure. In both hypertensive and normotensive animals counterpulsation diminished the magnitude of ST segment elevation from average control levels during occlusion of 3.0 ± 0.7 mv to 1.56 ± 0.34 mv following counterpulsation (P < .05).

**Discussion**

The results of the present study clearly indicate that myocardial contraction in ischemic areas of the left ventricle is depressed but not completely eliminated and that force development in these ischemic areas can be augmented by a positive inotropic agent, isoproterenol, or by arterial counterpulsation. Hood et al. (13) recently have shown that direct intracoronary injections of isoproterenol can produce an augmentation of the shortening rate of segments of ischemic muscle, and these findings are consonant with the augmentation of force observed in the current study. However, as indicated by the results of this and earlier studies (9), this augmentation of myocardial contractile state produced by isoproterenol occurred at the expense of an expanded area of myocardial damage. Thus
TABLE 3

Effects of Counterpulsation on Wall Stress during Ischemia

<table>
<thead>
<tr>
<th>Exp</th>
<th>HR</th>
<th>AoP mid-diast</th>
<th>LVEDP (mm Hg)</th>
<th>LVP (mm Hg)</th>
<th>Isom stress 1 (mV)</th>
<th>ST 1</th>
<th>Isom stress 2 (mV)</th>
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C 1 and Occ 1 = control and during initial coronary occlusion; ST = ST segment elevation from a representative epicardial site near the force gauge; Avg ST = average ST segment elevation from all sites. Cnp = steady state response to counterpulsation following coronary occlusion; P-Cnp = steady state response following cessation of counterpulsation; Isom stress 1 and 2 = force recorded from two sites (marginal areas) near the infarction.

*Gauges in normal myocardium.

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The fall in isometric wall force after occlusion within the ischemic area was greater after isoproterenol (P < 0.01), although a higher total level of isometric wall force within the ischemic area was maintained. In marginal areas, not previously influenced by the occlusion, force fell during isoproterenol infusion.

The observation that postextrasystolic augmentation of force frequently was diminished or abolished in ischemic myocardium suggests that the response to this type of isotropic stimulation was less well maintained during ischemia than the adrenergic mechanism. This finding would lend support to the view that calcium release from the sarcoplasmic reticulum may be impaired, or hypoxia may cause a reduction in the number of troponin-binding sites for calcium (14).

Two major benefits of circulatory assist have been emphasized in the past—the reduction of cardiac work and increase in coronary blood flow. There has been wide agreement concerning the effect of systolic unloading of the heart in diminishing myocardial oxygen consumption (15-21). Results have been conflicting in regard to alterations of coronary blood flow during counterpulsation, but an increase of coronary flow generally has been noted and a reduction in the infarct size has been observed (15-18, 22-25). Although it
Effects of counterpulsations on force development in the ischemic myocardium. Tracings obtained after coronary occlusion = Control 1 and Counterpulse 1 while the animal was "normotensive"; Control 2 and Counterpulse 2 after hemorrhagic "hypotension"; Isom F₁ and F₂ recorded from the ischemic myocardium; LVP = left ventricular pressure. The upper tracing shows injection (in) and withdrawal (out) phase of the pump. (Expt 18.)

is now recognized that alterations in coronary perfusion pressure within a certain range need not result in changes of coronary blood flow because of autoregulatory changes in the resistance of the coronary vascular bed (28–29), at lower coronary perfusion pressures both blood flow and the performance of the left ventricle appear to be perfusion pressure dependent (29, 30). Ischemic and marginal zones probably represent such areas in the myocardium. The immediate increase in local force development in hypotensive animals during counterpulsation supports the idea that the force improvement was primarily related to improved coronary flow, possibly through collateral channels such as postulated by Jacobey et al. (31) and Rosensweig and Chatterjee (24). It was also of interest that in the normotensive animals, the force development during counterpulsation improved at a much slower rate than in the hypertensive group. Thus, it is possible that in this group of experiments, the mechanism of flow improvement was different and represented the improvement in capillary exchange postulated by Goldfarb et al. (20).

In these experiments, care was taken to circumvent the dependency of isometric force recordings on intraventricular pressure and on alterations in left ventricular radius. Thus, as discussed earlier, and as shown by Newman and Walton (3, 4), the isometric force recording can be influenced by alterations in local wall radius during ischemia and by the effect of force development in normal tissue on the recorded isometric force. These effects may explain previous contradictory reports concerning the influence of coronary occlusion on local wall forces. In the present study, the buffer device eliminated nearly all of the forces acting on the pins in the opposite direction from that recorded by the isometric muscle segment. However, some influence of forces at right angles to the isometric muscle...
segment might still have occurred. Thus, during a brief episode of occlusion of the descending thoracic aorta performed prior to, during, and following myocardial ischemia, there was always a slight increase in isometric wall force. In no case, however, was the pressure alteration observed with coronary occlusion or during counterpulsation or isoproterenol infusion of sufficient magnitude to influence significantly the alterations in isometric wall forces observed experimentally. For example, the fall in LV pressure observed during coronary occlusion averaged 3 mm Hg, during counterpulsation 5.3 mm Hg, and from the aortic obstruction studies in these same animals an average fall of isometric force of less than 4% would have been expected. Nevertheless, force fell by 23.7% during coronary occlusion and actually increased during counterpulsation, indicating that the force developed by fibers within the gauge was the major factor influencing measured force. However, the aortic occlusion studies were performed with the ventricle developing some pressure, and it is difficult to totally exclude some effects of pressure development on the gauge. If this is the case it is likely that the decrease would have been even greater. It is also possible that alterations of gauge function due to the pins cutting the myocardium could have occurred during the experimental procedures. However, the stability of the force recording in normal areas (Table 1, col. NF) would not support this.

In summary, the present study has clearly indicated a significant reduction but not elimination of active myocardial wall force in ischemic zones following experimental coronary occlusion. Moreover, force could be augmented by either isoproterenol or counterpulsation, and counterpulsation can produce a significant improvement in function in the ischemic myocardium, while reducing the area of ischemic injury. The fact that isoproterenol can also augment the function of this tissue but extends the area of injury, carries important clinical implications.

Acknowledgment
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Observations on Factors Affecting Local Forces in the Left Ventricular Wall during Acute Myocardial Ischemia

Heinrich R. Schelbert, James W. Covell, John W. Burns, Peter R. Maroko and John Ross, Jr.

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