An Analysis of Myocardial Infarction

The Effect of Regional Changes in Contractility

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SUMMARY. In a preceding paper, we employed an initially spherical, modified membrane model of the infarcted ventricle to investigate the relation between ventricular function and both infarct size and infarct stiffness. In the present paper, we have applied the same model to a set of different questions, namely, the consequences of enhanced or depressed inotropic state within the noninfarcted myocardium. When infarcted ventricles containing up to 41% infarction are examined, stroke volume appears to be relatively insensitive to increases in inotropic state. However, stroke volume falls rapidly when inotropic state is depressed below 80% of normal. For the case of a ventricle with a large, weakly contracting segment which is not totally infarcted, stroke volume is impaired only when the contractility of the weak region is diminished below 50% of normal. Finally, the stress concentration around a region of infarction appears to be dependent more strongly on the inotropic state of the noninfarcted tissue than on the infarct size (Circ Res 55: 805–815, 1984).

IN our earlier model of the infarcted ventricle (Bogen et al., 1980), we considered infarction as an all-or-nothing state. That is, the infarcted region was considered to be totally devoid of contractile activity. Similarly, we did not address the question of whether increases in the contractility of noninfarcted myocardium could effectively compensate for the presence of the infarct.

In fact, there are a whole series of interesting questions relating to myocardial contractility or inotropy, especially if we take the view that infarction is only an extreme example of a regional decrease in contractile state. Infarction may also initiate, or be modified by, further changes in contractile states throughout the ventricle. For instance, in the post-myocardial infarction period, sympathetic and adrenergic stimulation may exert a positive inotropic effect which helps to restore pump function. On the other hand, catecholamine depletion in the myocardium may eventually render sympathetic stimulation ineffective and permit the heart to fail.

It is not our purpose to discuss under what circumstances these changes in inotropic state do occur, other than to indicate the importance of understanding their effects on cardiac function. Similarly, both positively and negatively acting inotropic agents may be administered by physicians to patients with myocardial infarction: positively acting inotropic drugs for heart failure or cardiogenic shock, and negatively acting inotropic drugs for the reduction of myocardial stress and oxygen demand.

To answer the question of what effect these changes in regional contractility might have on ventricular function, we adapted our previously developed model of the infarcted ventricle to allow regional variations in inotropic state. In particular, we considered two key questions: (1) how is cardiac function influenced by contractile changes in the noninfarcted myocardium, and (2) how is cardiac function influenced by the presence of a weakly contracting, but not totally infarcted, region. In each case, an evaluation of stroke volume and stresses within the heart was carried out.

Methods

The method of analysis employed here is essentially identical to that employed in Bogen et al. (1980) and is described in detail in that reference. The ventricle with weakly or noncontracting portions is modeled as an initially spherical, inhomogeneous, elastic pressure vessel. Emphasis is wholly on the determinants of stroke volume, rather than the determinants of such time-dependent quantities as the rate of ventricular pressure development or ejection. Hence, the calculations concern themselves only with cardiac deformation when the ventricle is in the end-diastolic or end-systolic state. Relying on the experimental evidence of Suga and Sagawa (Suga, 1971; Suga et al., 1973; Suga and Sagawa, 1974; Sagawa, 1978), we have argued that the peak isovolumic, end-systolic, and end-ejection pressure-volume (P-V) curves represent approximately identical load-independent relations. Thus, prediction of end-systolic volume involves only determination of the end-systolic P-V relation and knowledge of the end-systolic pressure. Similarly, end-diastolic volume is determined by the end-diastolic P-V relation and the end-diastolic pressure. In summary, cardiac stroke volume is determined completely by the end-diastolic and end-systolic pressure-volume relations, and by the end-diastolic and end-systolic pressure, which are operating parameters of the cardiovascular system. Analytically, therefore, the task is to compute the end-diastolic and end-
systolic relations for ventricles with weak or noncontracting regions.

It should be pointed out that, at present, the existence of a load-independent “end-systolic pressure-volume relation" for the diseased heart requires further experimental substantiation. Such clinical studies as that of Grossman et al. (1977) suggest the use of end-systolic P-V points as a clinical measure of ventricular contractility. The recent experimental investigations by Sunagawa et al. (1983) of the regionally ischemic dog heart also suggests the applicability of the end-systolic P-V relation to the diseased heart. However, it remains to be proven that diseased ventricles exhibit the same load-independence in their end-systolic state as do normal ventricles.

The model is formulated in the following fashion. The left ventricle is considered as an initially spherical structure. Strong and weak regions are disposed axisymmetrically, as illustrated in Figure 1. Because strong and weak regions of the heart represent areas of varying material properties, deformations are in general nonuniform, implying a nonspherical configuration at states other than the initial, zero-pressure, diastolic state (Fig. 1a). This is illustrated in Figure 1b.

The contractile nature of the cardiac muscle is incorporated into the model by the acknowledgment of two different constitutive descriptions of the muscle, one of which applies at end-diastole, and one of which applies at end-systole. Although, in actuality, there is a continuum of time-dependent material properties which is a more complete description of the contracting myocardium, the analysis here requires only a biphasic characterization of material properties. Since the end-diastolic and end-systolic pressure-volume curves are themselves static relationships, the constituent materials of the inhomogeneous ventricle requires only static, or elastic, descriptions. This observation specifically allows myocardial force-velocity relations to be neglected, since end-diastole and end-systole are modeled as zero-velocity states.

Furthermore, the elastic descriptions of both diastolic and systolic myocardium make use of the convenient power-law strain energy function formulation of constitutive properties. Accordingly, the strain energy function $\phi$ takes the form

$$\phi = \mu_p [\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3]$$

where the $\lambda$'s represent the extensions of the material (final length/initial length) in the three principal directions, and $\mu_p$ and $k_p$ are elastic constants of the material (the subscript p serves as a reminder that the strain energy function is assumed to be a power law). As shown by Ogden (1972), this form of the strain energy function implies the following uniaxial and biaxial stress-extension laws:

- uniaxial tension $\sigma = \mu_p [\lambda_1^{\alpha - 1} - \lambda_2^{\alpha - 1}]$
- biaxial tension $\sigma_{\alpha} = \mu_p [\lambda_1^{\alpha - 1} - \lambda_2^{\alpha - 1}]$, $\alpha = 1, 2$

where $\sigma$ is the “true" or Cauchy stress (force/deformed cross-sectional area).

According to this formulation of the myocardial constitutive law, the elastic constants $\mu_p$ and $k_p$ must vary not only with diastolic and systolic state, but with the metabolic condition, or contractility, of the myocardium. In transmural myocardial infarction, for instance, the affected region completely loses contractile activity, and thus must be represented by a single set of elastic constants which do not vary from diastole to systole. Moreover, these elastic constants may change over the long time course (hours to months) with the progression of infarct inflammation and scar formation. Hence, infarct elastic
properties are typically dependent upon the age of the infarct (Parmley et al., 1973). The representative range of infarct properties used in the present study is summarized in Table 1.

Since the present paper concerns itself with the effects of inotropic state on cardiac function, the elastic description of systolic myocardium needs to be considered in more detail. Examination of the power-law strain energy function given in Equation 1 and the corresponding stress-extension relations given in Equations 2 and 3 reveals the suitability of this formulation for representing highly non-linear materials such as diastolic myocardium. Diastolic myocardium is typically described by a high power-law relation, with \( k_p = 18 \) (Janz et al., 1976). When \( k_p \) is given the much lower value of \( k_p = 2 \), it is also a useful description of neo-Hookean, rubber-like materials under large deformations (Trelolar, 1975). The relation between developed tension and muscle length has been observed to be approximately linear in papillary muscles over the physiological range of extensions (Grimm et al., 1970). Thus, in the present investigation, developed systolic stress is described by Equation 3, with \( k_p \) taken as equal to 2. Since total systolic tension is the sum of developed tension and resting tension, normal systolic myocardium must then be described by a two-term constitutive relation, typically one term with \( k_p = 2 \) and the other with \( k_p = 18 \).

It should be mentioned at this point, in advance of the full description of systolic myocardium under the axial stress is given by the following relation:

\[
deviated stress: \sigma_s = \mu_s(\lambda_s \lambda_s^* - \lambda^3 \lambda^*_3) \quad (4)
\]

In this equation, \( \mu_s \) is the value given to \( k_p \) for the description of the developed stress; \( \lambda_s \) is the ratio of the diastolic rest length to the characteristic systolic rest length. Thus, the full description of systolic myocardium under the axial stress is given by the following relation:

\[
total stress: \quad \sigma = \mu_s(\lambda_s \lambda_s^* - \lambda^3 \lambda^*_3) + \mu_d(\lambda^d_s \lambda^d_s^* - \lambda^3 \lambda^*_3) \quad (5)
\]

where \( \mu_d \) and \( k_d \) are the values of \( k_p \) and \( k_p \) appropriate for resting myocardium.

As described previously, the characterization of infarcted myocardium entails setting \( \mu_s = 0 \) in the above equation. However, the elastic description of myocardium is not restricted to the limiting cases of contractile function considered in the earlier work of Bogen et al. (1980), i.e., the complete absence or presence of contractile function. Rather, if the symbol \( \mu_s^* \) is used to denote the value of \( \mu_s \) in normal myocardium, a value of \( \mu_s^* \) less than \( \mu_s^* \) but greater than zero denotes subnormal muscle contractility. In this case, contractile function is still present, since there is a change in material properties from diastole to systole. However, the stress generated at any level of extension (other than the zero-developed stress extension) will be less than normal. Similarly, supranormal contractility is described by values of \( \mu_s \) greater than \( \mu_s^* \). Therefore, the evaluation of inotropic changes in the ventricle proceeds by the examination of ventricular deformation and pressure-volume relations when \( \mu_s \) takes different values in different regions of the heart. Myocardial tension-length

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**Table 1**

**Summary of Computations for the Infarcted Ventricle**

<table>
<thead>
<tr>
<th>Infarct size</th>
<th>Infarct stiffness</th>
<th>End-diastolic volume at EDP = 12 mmHg</th>
<th>End-systolic volume for contractility ((\mu_s/\mu_s^*))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No infarct</td>
<td>1.86</td>
<td>-60% -40% -20% 0% +20% +40% +60%</td>
</tr>
<tr>
<td>15%</td>
<td>Immediate</td>
<td>2.0</td>
<td>1.86 1.75 1.11 0.99 0.93 0.90 0.88 0.86</td>
</tr>
<tr>
<td></td>
<td>Acute</td>
<td>7.9</td>
<td>1.80 1.69 1.08 0.96 0.91 0.88 0.86 0.84</td>
</tr>
<tr>
<td></td>
<td>Subacute</td>
<td>0.75</td>
<td>1.79 1.50 0.99 0.89 0.85 0.82 0.81 0.79</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>118</td>
<td>1.65 1.22 0.87 0.80 0.76 0.74 0.73 0.72</td>
</tr>
<tr>
<td>25%</td>
<td>Immediate</td>
<td>2.0</td>
<td>2.0 1.98 1.33 1.19 1.13 1.09 1.06 1.05</td>
</tr>
<tr>
<td></td>
<td>Acute</td>
<td>7.9</td>
<td>1.76 1.89 1.26 1.14 1.08 1.05 1.02 1.00</td>
</tr>
<tr>
<td></td>
<td>Subacute</td>
<td>0.75</td>
<td>1.75 1.56 1.10 1.00 0.96 0.93 0.91 0.90</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>118</td>
<td>1.55 1.19 0.89 0.83 0.79 0.78 0.76 0.75</td>
</tr>
<tr>
<td>41%</td>
<td>Immediate</td>
<td>2.0</td>
<td>2.0 2.28 1.68 1.53 1.46 1.42 1.39 1.37</td>
</tr>
<tr>
<td></td>
<td>Acute</td>
<td>7.9</td>
<td>1.70 2.17 1.58 1.44 1.38 1.34 1.32 1.30</td>
</tr>
<tr>
<td></td>
<td>Subacute</td>
<td>0.75</td>
<td>1.68 1.68 1.27 1.18 1.13 1.10 1.08 1.07</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>118</td>
<td>1.40 1.12 0.92 0.87 0.84 0.83 0.82 0.81</td>
</tr>
</tbody>
</table>

Effects of contractile function in the noninfarcted region are summarized for three infarct sizes, four infarct stiffnesses, and seven contractile states.
relations corresponding to variations in $\mu_s$ are illustrated in Figure 2.

The value of $\mu_s^*$, normal contractility, deserves some discussion here. As in the earlier study (Bogen et al., 1980), $\mu_s^*$ is chosen to be the value which results in a maximal developed pressure of 250 mm Hg in the spherical homogeneous model of the normal ventricle. Since the choice of this value for $\mu_s^*$ is somewhat arbitrary, the evaluation of the results given in Bogen et al. (1980) would be aided by a sensitivity analysis of $\mu_s^*$. However, the results given in this paper do accomplish just that by examining cardiac inotropic agents may affect the myocardial force-velocity relations corresponding to variations in $\lambda_s$ are illustrated in Figure 2. The family of systolic tension-length curves corresponds to variations in myocardial contractility or the value of $\mu_s$. Note that increasing contractility produces a greater wall tension at any given length, but does not affect the systolic zero-stress length.

Assumptions and Limitations

The ventricular model described above makes several simplifying assumptions which require further comment. To begin with, the heart is represented as isotropic, regionally homogeneous, and initially spherical. This description is made in spite of a detailed view of the ventricle as a complex, oriented-fiber network covering a nonspherical geometry.

Aside from analytical convenience, there is reason to take the simple spherical model as a first approximation. The ventricle may not be as impenetrably complex as it first appears. For instance, nonuniformities in ventricular wall thickness and curvature are not separate complications, since they effectively compensate for one another. The ratio of wall thickness to total curvature is virtually constant over the ventricular surface (Woods, 1892; Role et al., 1978), suggesting that the average stress level in the ventricle is everywhere the same. The spherical, uniform-thickness model also preserves this feature of uniform stress.

Similarly, it appears that the nonspherical ventricular shape and the distribution of fiber angles are not isolated complexities. They may also compensate for one another. If the ventricle is represented as an ellipsoid of revolution, with a major-to-minor axis ratio of 2:1, the ratio of circumferential to longitudinal tension, at the equator, is approximately 7:4. In addition, the distribution of fibers at the equator is such that the predominant orientation of fibers is circumferential rather than longitudinal (Streeter et al., 1969). Since the number of fibers in a given direction thus tends to balance the tension borne in that direction, it would seem that each fiber, regardless of orientation, must carry the same tension or stress.

The above argument is only approximate, and does not take into account nonuniformities in stress due to the appreciable thickness of the ventricular wall. However, the argument demonstrates a possible structural principle of the ventricle: that of uniform (or near-uniform) fiber stress. The simple spherical model, with its uniform surface stress, is certainly consistent with this principle. A completely different model of ventricle, a fiber-wound cylinder (Arts et al., 1982) further supports the notion of uniform fiber stress, demonstrating that, in some instances at least, simple and complex models can give the same answers.

Besides the explicit assumptions concerning cardiac geometry and isotropy, the present model contains several implicit assumptions. One of these is the implicit neglect of bending moments. The modified membrane analysis foregoes a detailed description of the distribution of deformation and stress across the ventricular wall. When the model ventricle includes a weak region, as shown in Figure 1b, little bending actually occurs. This implies that the deformation is governed primarily by membrane stresses. When the model ventricle includes an infarct, as shown in an earlier paper (Needleman et al., 1983; Fig. 2b), significant bending is localized to the interface between normal and infarcted myocardium. This edge effect appears to have little influence on the calculated pressure-volume curves. [Again, see Needleman et al. (1983) for a comparison between the modified membrane model and thick-walled models.]

Bending should also have little influence on calculated stress concentrations around the abnormal region. This is because the weak or infarcted region induces an elevated circumferential stress, whereas localized bending occurs in the longitudinal direction. A more significant assumption concerns our description of infarcted and weak regions. We have considered only axisymmetric apical infarcts or weak regions, and we have considered only such regions which are clearly and dis-
continuously demarcated from normal tissue. We have not attempted to model either irregular, nonapical infarcts or transition regions between infarcted and noninfarcted tissue. Nonapical or indistinct infarcts may behave differently than the ones we have modeled here.

**Results**

**Effect of Inotropic State of Residual Myocardium**

One of the questions considered in Bogen et al. (1980) regards the adequacy of different physiological compensations in counteracting myocardial infarction. Although the Frank-Starling mechanism and tachycardia were shown to be powerful mechanisms of cardiac reserve, the role of increased inotropic state in the noninfarcted region, either as a consequence of increased sympathetic activity or as a consequence of pharmaceutical intervention, was left unstated. In the computations described below, an effort is made to evaluate such inotropic compensations.

End-systolic P-V relations were calculated in the infarcted ventricle for infarcts ranging in size from 15% to 41% of the ventricular surface, for infarcts of varying age and elasticity, and for inotropic states in noninfarcted myocardium deviating up to 60% above and below normal contractility ($M^*$). The results of these calculations are summarized in Figures 3 and 4 and Table 1. It should be noted that the predicted end-systolic P-V curves are not perfectly linear, either for the normal or the infarcted case. However, over the end-systolic pressure range of 60–120 mm Hg, the relations are approximately linear, so that the curves can be characterized by their local tangent slopes in that region.

Figure 3 displays calculated end-systolic P-V relations in a ventricle containing an extensible, acute infarct. P-V relations are plotted for three sizes of infarct (15%, 25%, and 41%) and in each case for normal and +20% supranormal inotropy in the noninfarcted region. Figure 4 is a similar plot, but in this case, only the large 41% infarct is considered, and the P-V relations are drawn for the infarcts of different ages having the material properties described in Table 1. It should be pointed out here that the chronic infarct represents a very old, scarred region of tissue which is quite inextensible. The subacute infarct is more recent, of the order of a week post-infarction, and is considerably more extensible. The acute and immediate infarcts are only hours or minutes old, respectively, and are still more highly distensible. The immediate infarct is given properties identical to those of normal diastolic tissue.

To evaluate these curves, one must recall that, in conjunction with end-systolic pressure, they are the determinants of the final volume in the ventricle at the end of contraction. If the end-systolic pressure is taken to be, say, 100 mm Hg, the intersection of the P = 100 mm Hg line with the end-systolic P-V curve gives the end-systolic volume. Thus, in Figures 3 and 4, the effect of a 20% added inotropy is an increase in the slope of the P-V relation and a decrease in the end-systolic volume. Inspection of Figure 3 reveals that, for a given infarct type, the shift in end-systolic volume resulting from an increase in inotropy is little affected by the infarct size: the horizontal distance between the broken and solid curves at the level of 100 mm Hg is about the same for the 15%, 25%, and 41% infarcts. However, Figure 4 shows that the shift in end-systolic volume is somewhat greater for the more extensible infarcts, such as the immediate infarct, than it is for the inextensible, chronic infarct.

This idea is clarified in Table 1, which provides a tabulation of the end-systolic volumes for some of the many cases calculated, based on an end-systolic pressure of 100 mm Hg. For the case of the 41% infarct cited earlier, the 20% increase in inotropy results in an end-systolic volume (ESV) shift from
The infarcted region is assumed to have mechanical properties corresponding to the immediate, subacute, acute, and chronic conditions. Infarcts of three sizes are shown: 15% (panel a), 25% (panel b), 41% (panel c), of the myocardial surface. These calculations and the ones in subsequent figures assume an end-systolic pressure of 100 mm Hg and an end-diastolic pressure of 12 mm Hg.

![Figure 5](http://circres.ahajournals.org/)

**Cardiac Function in the Presence of Weakly Contracting Regions**

Cardiac function may be impaired by a local reduction in myocardial contractility due to ischemia or some other disease process. In the present analysis, such weakly contracting regions are modeled as regions with reduced inotropic constant \( n_5 \). In general, the presence of such a weakly contracting region results in a depression of the end-systolic pressure-volume relation. The degree of systolic depression is directly related to the size of the affected region, and to the reduction in contractility in that region. This information, based on the calculations described in this paper, is summarized in Figure 7, which plots calculated stroke volume vs. the contractile state of the weak region for three regions of different size. Again, this calculation assumes an end-systolic pressure of 100 mm Hg and an end-diastolic pressure of 12 mm Hg. Since it further has been assumed that there is no alteration in diastolic properties in the affected regions, changes in stroke volume represent changes only in the end-systolic P-V relations.

Figure 7 shows, as expected, that for a given reduction in local contractile function, the larger the affected area, the larger the reduction in stroke volume. However, an unanticipated result is that, for all infarct sizes, stroke volume is relatively insensitive to reductions of local contractility up to 50%. Beyond that level of reduction, stroke volume becomes much more sensitive to further inotropic depression. For example, in the case of a 41% weak region, the first 50% loss in contractility results in a reduction in stroke volume of 7%. However, loss of state of the noninfarcted region has been defined in terms of the percentage deviation from normal inotropic level. Hence, the zero value corresponds to normal inotropy, positive values to supranormal, and negative values to subnormal. The −100% level (not shown) would represent complete absence of contractile function.

One important conclusion from Figures 5 and 6 is that infarct size is not an important determinant of cardiac responsiveness to supranormal levels of inotropy. This result follows from examination of the slopes of the stroke volume vs. contractile state curves. The slopes of these curves, which are a measure of inotropic sensitivity, are essentially the same for all three sizes of infarct of a given type at supranormal inotropic levels (compare the slopes of the three curves in the right half of each part of Fig. 6).

However, Figures 5 and 6 show that, although stroke volume is relatively insensitive to supranormal inotropic state, stroke volume begins to drop off rapidly for subnormal levels of inotropy below −20%. For example, in the case of the 41% acute infarct, an increase in inotropy of 40% results in only a 5% improvement in stroke volume, with respect to the noninfarcted heart, but a 40% decrease in inotropy results in an 18% loss in stroke volume.
the remaining 50% contractility would result in a further 58% reduction in stroke volume, so that the heart would be pumping only 35% of its normal stroke volume.

**Stress Concentration and Inotropy**

Results of calculations presented in Bogen et al. (1980) showed the presence of a region of high circumferential stress in the border zone of an infarct. The existence of such elevated systolic stresses in the noninfarcted myocardium adjacent to the infarct may be a significant determinant of the ultimate size of a developing infarct, because the elevated stress can be expected to lead to increased oxygen demand (see Discussion). Consequently, calculations were made to determine the relation between the inotropic state of the noninfarcted region and the stress level in the border zone. The results are shown in Figure 8, in which stress concentration is plotted against inotropic state for different types and sizes of infarct. Here, stress concentration has been defined as the ratio of the maximum circumferential border zone stress to the minimum circumferential stress level at a point furthest from the infarct. These stresses are evaluated at an end-systolic pressure of 100 mm Hg.

As shown by Figure 8, the stress concentration, although increasing significantly with increasing inotropy, is not affected strongly by infarct size. In comparison, the stress concentration is radically affected by infarct elasticity. For example, for a heart with normal inotropic state having a 41% infarct, the stress concentration is 2.0 for a stiff chronic infarct but is 3.9 for an extensible immediate infarct. Increasing the inotropic state by 60% results in stress concentrations of 2.9 and 5.2 for the chronic and immediate infarcts, respectively.

Stress concentrations also occur in the border zone
surrounding regions of myocardial weakness, or diminished contractility. Figure 9 illustrates the dependence of stress concentration on the contractile state of weak myocardial regions ranging in size from 15% to 41%. As is apparent, the size of the weak region has little effect on the stress concentration. Perhaps the most significant observation is that stress concentration is most markedly increased when the contractile state of the weak region drops below 50%.

Redefinition of $\mu_0^*$

The results contained in Figures 3–9 are referenced to a "normal" inotropic state defined as that inotropic state which yields a maximum end-systolic pressure of 250 mm Hg. If it is desired to redefine "normal" inotropic state, the conversion can be made as follows. When the normal level $\mu_0$ is taken as $\mu_0^*$, the inotropic index $I^*$, or percentage change in inotropy, is given by

$$I^* = \frac{\mu_0^* - \mu_0}{\mu_0^*}.$$ 

A new inotropic index $I^{**}$ can be defined, with $\mu_0^{**}$ as the normal value for $\mu_0$, by

$$I^{**} = \frac{\mu_0^* - \mu_0^{**}}{\mu_0^{**}}.$$ 

Then $I^{**}$ is related to $I^*$ by

$$I^{**} = \frac{\mu_0^*}{\mu_0^{**}} (I^* + 1) - 1.$$ 

Discussion

Sensitivity of Stroke Volume to Inotropic State in the Infarcted Ventricle

The two remarkable things about the calculated relationship between inotropic state and stroke volume in the infarcted ventricle are the insensitivity of stroke volume to supranormal levels of inotropy and the presence of a "knee" in the stroke volume-inotropy curve. To appreciate the insensitivity to
supranormal inotropy, one should compare the effects of supranormal inotropy with those derived from increased diastolic filling (the Frank-Starling mechanism) and increased heart rate, other mechanisms of restoring cardiac output following myocardial infarction.

As shown in Bogen et al. (1980), for an acute, 41% infarct, the calculated reduction in stroke volume is 72%, when end-diastolic pressure is held at 12 mm Hg. If the filling pressure is allowed to rise to 24 mm Hg, a 29% recovery in stroke volume can be achieved; that is, at maximum end-diastolic pressure (EDP) the net loss in stroke volume is 43%. On the other hand, if the EDP is returned to 12 mm Hg and the rate is allowed to double instead, a 28% recovery in cardiac output can be achieved. In contrast, increasing inotropy by 60% will result in a stroke volume recovery of only 8%. Even if inotropy were increased by 100%, so that the noninfarcted myocardium was twice as strong, the stroke volume recovery would be only 11%.

This is a very modest augmentation in stroke volume for what is essentially maximal cardiac inotropy. Such a doubling of contractility is achieved only by significant reflex or pharmaceutical action. For instance, in the dog, extreme sympathetic and adrenal discharge, such as that resulting from cerebral ischemia, can increase inotropic state by 137% (Suga et al., 1976). Similarly, in a denervated canine preparation, the infusion of epinephrine (2 μg/kg per min) can increase inotropic state by 85% (Suga et al., 1973).

Why is supranormal inotropy such an ineffective compensation for myocardial infarction? The answer is found by considering the shape of the stroke volume vs. inotropy curve (Figs. 5 and 6), and, in particular, the presence of the "knee." The sensitivity of stroke volume to inotropic state is actually a function of the two other separate sensitivities. The first is the sensitivity of stroke volume to the slope of the end-systolic pressure-volume relation, and the second is the sensitivity of the end-systolic P-V slope to the inotropic state of the myocardium.

To consider the first effect it is helpful to refer to Figure 10. Here a number of hypothetical end-systolic P-V relations are displayed. The intersections of these lines with the horizontal end-systolic pressure line defines the end-systolic volumes, as indicated by the vertical lines. Because we have assumed straight lines through the origin, as the slope of the end-systolic line is reduced, the corresponding end-systolic volume is increased. In general, the relation between the slope of the end-systolic P-V line and the end-systolic volume (ESV) is hyperbolic. For the schema shown in Figure 10, where the end-systolic P-V lines intersect at zero volume, ESV = ESP/Ees, where Ees is the end-systolic elastance, or the slope of the end-systolic line, and ESP is the (assumed constant) end-systolic pressure. Consequently, the sensitivity of ESV to changes in Ees is d(ESV)/d(Ees) = ESP/Ees. This result indicates that when Ees is reduced, i.e., the end-systolic relation depressed, ESV is more sensitive to changes in Ees. This is seen in Figure 10, in which there are two sets of the end-systolic P-V lines. Each set is in turn comprised of two lines which differ by a given Ees. The resulting change in ESV for the given change in Ees is much larger for the rightward, or depressed, end-systolic lines.

These observations effectively explain the basic shape of the stroke volume vs. inotropy curves in Figures 5 and 6. Even so, there is still the matter of
the sensitivity of the ventricular elastance, $E_{es}$, to changes in inotropy. Because this sensitivity is dependent on both infarct size and elasticity, it can be determined only through a case-by-case calculation. One could postulate that the more-elastic infarcts would tend to dissipate some of the beneficial effects of added inotropy by increased stretching of the infarct. Indeed this impression is confirmed by analysis of the results given in Figure 4.

**Sensitivity of Stroke Volume to the Inotropic State of Weak Myocardial Regions**

The fact that cardiac stroke volume is little affected by regional inotropic reductions of up to 50% reveals new aspects of cardiac reserve. According to this result, a partial malfunction of a sizable portion of the myocardium is effectively compensated, with respect to stroke volume, by the remaining normally functioning myocardium. It is important to point out that such compensation occurs instantaneously, involves no functional changes in the regions of normal inotropy, and would not be detectable by simple measurements of cardiac function. Although this insensitivity to local reduction in inotropic state is perhaps beneficial to cardiac function, it also poses a problem in cardiac diagnosis. That is, significant derangement in myocardial function will not necessarily become apparent from the usual sorts of hemodynamic observations, including peak ventricular pressure and ejection fraction.

**Stress Concentration and Inotropic State**

In Bogen et al. (1980), it was pointed out that the calculation of stress concentrations based upon a membrane formulation of ventricular mechanics will yield an estimate of the actual stress concentration, rather than an exact value. We repeat the same caution here; however, in the results presented in this paper, the magnitude of the predicted stress concentration surrounding infarcted or weakly contracting regions is so great (up to a value of 5) that there can be little doubt of the ability of myocardial inhomogeneities to induce important regions of stress concentration. As shown in Bogen et al. (1980), the region of elevated circumferential stress surrounding the inhomogeneity is not confined to a small boundary region adjacent to the inhomogeneity. Rather, elevated circumferential stress is seen to extend throughout a sizable portion of the ventricle.

This result is important because of the increased oxygen demand which attends increased myocardial stress. In a heart in which coronary vascular disease is present, increased oxygen demand may result in eventual myocardial ischemia, which in turn may result in angina pectoris, myocardial infarction, or cardiac arrhythmia. Consequently, the relation between myocardial stress and inotropic state (Figs. 8 and 9) is especially important clinically. As shown in Figure 8, the myocardial stress can attain values between 2 and 5 times normal when a drug is given which increases inotropy by 50%, regardless of the size of the infarcted region. The augmentation in stress due to the 50% increase in inotropy appears to be independent of infarct type, and is approximately equal to the normal end-systolic stress level. There may be circumstances (reduced coronary blood flow) under which this large an increase in stress and oxygen demand in the border zone poses an unacceptable risk of extension of the infarcted region.

Moreover, consideration of the stress concentration surrounding a myocardial weak region raises the possibility of an unstable process contributing to the progression of regional ventricular ischemia. That is, as local myocardial contractility drops below 50%, circumferential border zone stress sharply increases (Fig. 9). As the border zone stress increases, so does oxygen demand. If the increase in oxygen demand is sufficiently great, border zone ischemia becomes a possibility. Furthermore, such border zone ischemia may be attended by a reduction in border zone contractility, thus effectively increasing the area of myocardial weakness and producing a still larger border zone with increased stresses. As outlined above, this process is unstable. It is, however, limited by the fact that when enough myocardium becomes involved, ventricular pressure will eventually fall, thus reducing myocardial stress and oxygen demand. Whether this mechanism actually contributes to the progression of myocardial ischemia is purely conjectural at this state. Nevertheless, an instability due to stress-induced ischemia remains a possibility.

**Conclusions**

There are several interesting and potentially important implications of the analytical results presented here. First of all, there is the prediction that relatively small increments in stroke volume can be achieved by supranormal contractile stimulation in the infarcted heart. At the same time, such inotropic stimulation augments the myocardial stress concentration in the border zone surrounding the infarct. On the other hand, subnormal levels of myocardial contractility drastically reduce stroke volume in the infarcted heart. The conclusion is that there are diminishing returns for inotropic stimulation in myocardial infarction. Inotropic stimulation will most likely be beneficial if the myocardium shows depressed contractility, assuming that the myocardium is still responsive to the inotropic agent.

The study of myocardial weak regions offers the surprising conclusion that substantial mechanical abnormalities can occur in the heart without greatly affecting stroke volume. Contractility must be reduced below 50% before such abnormalities can be clinically apparent. Moreover, consideration of the stress concentration surrounding a myocardial weak region raises the possibility of an unstable process...
Bogen et al. / Model of Regional Contractility

contributing to the progression of regional ventricular ischemia.

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