Effect of Acute Volume Load on Refractoriness and Arrhythmia Development in Isolated, Chronically Infarcted Canine Hearts

Hugh Calkins, MD, W. Lowell Maughan, MD, Harlan F. Weisman, MD, Seiryo Sugiura, MD, Kiichi Sagawa, MD, and Joseph H. Levine, MD

In normal isolated, perfused canine ventricles, increased ventricular volume leads to shortening of refractoriness. To test the hypothesis that myocardium within an infarction zone is more susceptible to volume-induced changes in refractoriness than is normal myocardium, we measured strength-interval curves at low and high end-diastolic volumes at control and infarcted sites in 14 isolated, blood perfused, canine hearts with chronic (>25 days) infarctions. In addition, the effect of volume load on inducing ventricular arrhythmias was studied at one to six sites in 11 hearts. Differences in refractoriness and inducibility at low (22±5 ml) and high (48±6 ml) end-diastolic volumes were compared. At control sites, volume load reduced the absolute refractory period from 178±16.5 to 175±16.7 msec (p<0.05), but no significant change in the relative refractory period occurred. At infarcted sites, the change in refractoriness with volume load was greater, and the absolute refractory period decreased from 171.5±21 to 160.6±26.3 msec (p<0.01), and the relative refractory period decreased from 180.1±22.1 to 169.9±26 msec (p<0.05). This differential effect of volume load on refractoriness led to an increased dispersion of overall refractoriness at high volume. Infarcted sites showing the largest changes in refractoriness were characterized by patchy scars extending at least to the midmyocardium, whereas sites located within areas of transmural scar, endocardial scar, or rare microfoci of fibrosis showed no increased sensitivity to volume load. Of eight hearts in which no tachyarrhythmias were inducible during programmed electrical stimulation at low volume, four had tachyarrhythmias induced at high volume. Sites of stimulation associated with a conversion from noninducible to inducible tachyarrhythmias showed a larger degree of shortening of refractoriness (change in absolute refractory period: 24.7±16.5 vs. 3.9±6.5 msec, p<0.05). These data indicate that volume loading may have electrophysiologic significance and that it may be of greater functional importance under pathologic conditions. (Circulation 1989;79:687–697)

Patients with congestive heart failure have a high mortality related, in part, to a high incidence of arrhythmias and sudden death.1–3 Although the physiologic basis of these arrhythmias is unknown, they occur frequently in conditions with elevated wall stress, increased volume load, and regional wall motion abnormalities.4–5 The mechanism of this association between these mechanical factors and arrhythmias has not been determined. Contraction-excitation feedback, the phenomenon whereby changes in the mechanics of myocardial contraction precede and result in changes in membrane potential, may contribute to arrhythmias. Alterations in the action potential duration, diastolic potential, conduction velocity, and automaticity have all been described under different loading conditions in myocardial tissue.6–11 These studies, however, were performed primarily in normal isolated tissues or under non–steady state conditions in intact normal hearts. The purpose of our study was to investigate this phenomenon in chronically infarcted canine ventricles, a model that may simulate the abnormal, scarred hearts in which malignant arrhythmias and congestive heart failure...
frequently anatomic coexist. In addition, we hoped to define the anatomic substrate for each volume load and in this way show that there are anatomic and electrophysiologic correlates present, which are consistent with contraction-excitation feedback. We hypothesized that tissue within the infarcted zone would be more sensitive to a given volume load than control tissue outside the infarct because of a relatively greater increase in wall stress at the interface or border zone of scar and noninfarcted tissue. Therefore, we predicted that exaggerated load-dependent shortening of refractoriness would be most frequently detected in infarcted tissue with a large border zone surface area, that is, in large mottled infarcts. We further hypothesized that inducibility of ventricular tachyarrhythmias would be greater at high volume load, perhaps because of resultant greater dispersion of refractoriness due to these differential effects of load.

The purpose of our study, therefore, was twofold. The first purpose was to evaluate the differential effect of load change on refractoriness in normal and infarcted zones of chronically infarcted canine hearts and to correlate these changes with local pathologic conditions. Our second purpose was to evaluate the effect of increased volume load on inducing ventricular tachyarrhythmias.

Methods

Preparation of Canine Infarction

The techniques used in this study have been previously described. Seventeen preconditioned mongrel dogs (weight, 20–25 kg) were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and mechanically ventilated with room air. Under sterile conditions, a left lateral thoracotomy was performed, and the heart was exposed. The anterior descending coronary artery was ligated, and a silk tie was placed immediately distal to the first diagonal branch. Large apical branches of the circumflex artery were tied off. All dogs then underwent 30 minutes of partial occlusion of the anterior descending coronary artery, followed immediately by 2 hours of total occlusion and then reperfusion. Hyperemia distal to the occlusion site was evident in each case. Dogs were treated with lidocaine (2 mg/kg i.v.) at the time of total occlusion and 5 minutes before release. If ventricular fibrillation occurred (usually 15–25 minutes after total occlusion), the hearts were defibrillated immediately. The chests were then closed, and routine postoperative care was administered, which included prophylactic penicillin and streptomycin intramuscularly on the operative day and followed by oral penicillin for the first 7 postoperative days. Fourteen of 17 dogs survived this procedure.

Isolated Heart Preparation

Twenty-three to 36 days (mean, 30 days) after the heart was infarcted, it was isolated and supported by another dog by the techniques of Maughan et al. In brief, the 14 chronically infarcted donor dogs and 14 mongrel support dogs (weight, 20–29 kg) were anesthetized with sodium pentobarbital (30 mg/kg i.v.). A median sternotomy was performed on the infarcted donor dogs. The left subclavian artery of the donor dog was isolated and connected by tubing to the femoral arteries of the support dog. The brachiocephalic artery was cannulated for measurement of coronary arterial pressure. The azygous vein, superior vena cavae, inferior vena cavae, and descending aorta were ligated. Isolation was completed with ligation of the pulmonary hilus at which time cross circulation was begun. The heart was removed from the chest and was suspended above a funnel, and the left and right ventricles were vented. Coronary venous return drained into the funnel and was returned to the femoral vein of the support dog by plastic tubing.

A thin latex balloon mounted on a metal adaptor was sewn to the mitral valve anulus. The balloon adaptor was then connected to a ventricular volume control servopump system. A constant volume of tap water filled the pump and balloon (55 ml, unstressed volume). The servopump consisted of a linear motor (Model 411, Ling Electronics, Herts, England) that controlled the piston position of a rolling-diaphragm cylinder (Model SS-4-F-SM, Bellfom, Burlington, Massachusetts). A linear displacement transducer (Model 240–000, Trans-Tek, Ellington, Connecticut) sensed the position of the piston and produced a signal proportional to the balloon volume. This signal was used in a negative feedback loop for comparison with a volume command signal that represented the desired instantaneous ventricular volume. The error signal resulting from this comparison was supplied to a power amplifier (Model DC-300, Crown International, Elkhart, Indiana) that then drove the linear motor. Ejecting beats could be produced with an impedance loading system that imposed a simulated arterial hydraulic impedance on the ventricle.

Coronary arterial pressure was measured with a catheter placed in the aortic root. A perfusion servopump (Model 1215, Harvard Apparatus, Natick, Massachusetts) maintained a mean coronary arterial pressure of 80–90 mm Hg. Coronary arterial blood temperature was maintained at 38°C with a water bath and heat exchanger. Instantaneous volume could be monitored by measuring the linear displacement of a transducer that sensed the position of the piston as described above. Ventricular pressure was monitored by a pressure-tipped catheter (Millar Instruments, Houston, Texas) positioned in the left ventricular cavity 1 cm below the adaptor ring. These signals were fed to a storage oscilloscope (Model 5103, Tektronics) to monitor, on-line, the pressure-volume relation.

Coronary arterial pressure, left ventricular pressure and volume, an amplified bipolar electrogram (filtered at 40–400 Hz), and the support dog's systolic and diastolic atrial pressures were recorded.
on an ink jet recorder at 50 mm/sec (Model 2800, Gould, Cleveland, Ohio).

Although blood type incompatibility has been noted, though rarely, in these preparations, we do not believe this was a problem in any of the experiments in this series.

**Measurements of Excitability, Refractoriness, and Inducibility**

Refractoriness and excitability were determined by unipolar cathodal stimulation with 4-msec pulses. The indifferent anode was attached to the remaining pericardial or great vessel tissue. Once threshold excitability was determined, strength-interval curves were constructed as follows. After a 10-beat drive train (cycle length, 400–450 msec), an extra stimulus (current strength just above threshold) was introduced in late diastole (>250 msec). The coupling interval was decreased by 10 msec until capture no longer occurred. The coupling interval was then increased by 10 msec and decreased by 2 msec until capture was again lost. The milliamperage of the extra stimulus pulse was then increased until capture occurred, and the coupling interval was decreased again by 2 msec until capture no longer occurred. This sequence was repeated to a maximum current of 10 millamps. The absolute refractory period (ARP) was defined as the longest coupling interval at which a current of 10 mA failed to capture. The relative refractory period (RRP) was defined as the coupling interval at which an increase in current greater than 0.1 millamp was required to shorten the coupling interval by 4 msec.

Programmed electrical stimulation was performed with unipolar cathodal stimulation with 4-msec pulses at a current strength twice diastolic threshold. A 10-beat drive train at a cycle length of 350 msec was followed by a single extra stimulus introduced at a coupling interval of 250 msec. The coupling interval of the single extra stimulus was decreased by 10 msec until the refractory period was reached. If no sustained tachycardias were induced, the coupling interval of the first extra stimulus was increased by 50 msec, and a second extra stimulus at an equal coupling interval was introduced. The coupling interval between the first and second premature beats was then shortened by 10 msec until the second extra stimulus did not capture. The coupling interval of the first extra stimulus was then decreased by 10 msec until the second extra stimulus evoked a response. This sequence was repeated until refractoriness was reached or until sustained arrhythmias were induced. Endpoints of programmed electrical stimulation were ventricular fibrillation or sustained ventricular tachycardia (longer than 30 seconds).

**Experimental Protocol**

After isolation and stabilization of the chronically infarcted canine ventricle, multiple unipolar plunge electrodes were placed in the distributions of the circumflex coronary artery (control zone, \( n = 1.5 \pm 0.7 \)) and the anterior descending coronary artery (infarcted zone, \( n = 3.5 \pm 2.2 \)). The indifferent anode was attached to the remaining pericardium or great vessel tissue. The heart was then ventriculically paced at a cycle length of 400–450 msec, and a low- and high-volume range was determined for each heart. Results were that at low volume, a peak systolic pressure of 40–80 mm Hg was generated with an end-diastolic pressure less than 10 mm Hg, and at high volume, the peak systolic pressure was approximately two times that at low volume. Once the low- and high-volume range was determined for a given heart, an identical protocol was followed at each site of stimulation.

The heart was paced with unipolar cathodal stimulation at a cycle length of 400–450 msec at the predetermined low end-diastolic volume for that heart. Hemodynamic measurements were recorded, and the strength-interval relation at low volume was determined. The end-diastolic volume was then increased by 20–30 ml to the predefined high end-diastolic volume, and the strength-interval relation was determined again. To document reproducibility and, therefore, electrophysiologic stability of the preparation over time, the end-diastolic volume was decreased to the initial volume, and the strength-interval relation was redetermined. Acceptable reproducibility was defined as a difference in the absolute refractory period of less than or equal to 2 msec between two low- or high-volume determinations. At 60% of sites, reproducibility criteria were not met on initial return to low volume, and the strength-interval relation was redetermined at alternating high and low end-diastolic volumes until our reproducibility requirement was met. Programmed electrical stimulation was performed immediately after measuring refractoriness at 1–6 (mean, \( 2.8 \pm 1.6 \)) sites in the 11 infarcted hearts that did not show ventricular fibrillation during determination of the strength-interval curve at low volume. Programmed electrical stimulation was initially performed at low volume. In the eight hearts that were noninducible at low volume, programmed electrical stimulation was then performed at high volume. If sustained ventricular tachycardia or fibrillation was induced with an increase in diastolic volume, programmed electrical stimulation was repeated at low volume to assure stability of baseline inducibility.

**Postmortem and Histologic Methods**

After completion of the experimental protocol, the hearts were arrested in diastole with potassium chloride and cut into transverse slices (1–1.5 cm thick) with the plunge electrodes still in place. Outlines of the rings and the infarcted region were traced on a transparent plastic sheet. The chronically infarcted regions were identified on gross examination and were verified with subsequent histologic analysis. The tracings were planimetered for total area and area of infarcted myocardium. The total mass of the infarcted myocardium was comp-
TABLE 1. Hemodynamic Measurements

<table>
<thead>
<tr>
<th></th>
<th>End-diastolic volume (ml)</th>
<th>End-systolic volume (ml)</th>
<th>Peak systolic pressure (mm Hg)</th>
<th>End-diastolic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control zone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low volume</td>
<td>22.5±5.1</td>
<td>15.7±5.8</td>
<td>52.2±18.3</td>
<td>5.1±7.6</td>
</tr>
<tr>
<td>High volume</td>
<td>48.6±6.0</td>
<td>33.3±6.9</td>
<td>106.3±23.4</td>
<td>26.7±10.9</td>
</tr>
<tr>
<td>Infarct zone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low volume</td>
<td>22.2±4.7</td>
<td>14.9±4.7</td>
<td>59.9±18.1</td>
<td>6.3±7.6</td>
</tr>
<tr>
<td>High volume</td>
<td>47.8±5.9</td>
<td>30.6±6.1</td>
<td>115.8±18.2</td>
<td>26.2±13.6</td>
</tr>
</tbody>
</table>

Values are mean±SD.

Computes by multiplying the fractions of infarcted myocardium by the mass of each of the rings. The hearts were fixed in 4% neutral-buffered formaldehyde for 3–7 days, at which time the plunge electrode positions were determined. Transmural slices of myocardium 1–2 mm thick encompassing each plunge electrode site were embedded in paraffin, cut into 5-μm sections, and mounted on glass slides. These slides were stained with hematoxylin-eosin and Masson’s trichrome. They were read by one of the investigators who was unaware of which sections were infarcted or of the electrophysiologic variables recorded (H.F.W.) and were classified by the amount and pattern of fibrosis.

Statistical Methods

All data are expressed as mean±SD. Means were compared with paired or unpaired t tests corrected when necessary for lack of normal variance. Non-parametric tests (Wilcoxon’s rank series) were performed when t tests were inappropriate because of a lack of normal distribution. Analysis of variance was performed when more than two groups were compared. Correlations were performed with standard linear regression techniques. For all cases, a p value of 0.05 or less was considered significant.

Results

The hemodynamic intervention that we imposed on the chronically infarcted canine hearts is summarized in Table 1. During ventricular pacing at a drive train cycle length of 400–450 msec at control zone sites, end-diastolic volume was increased from 22.5±5.1 to 48.6±6.0 ml. This was associated with an increase in the peak systolic pressure and end-diastolic pressure. Similar increases in diastolic volume, end-diastolic pressure, and peak systolic pressure were obtained while pacing from control or infarcted sites.

Effect of Volume on Refractoriness

Figure 1 contains strength interval relations obtained at low and high end-diastolic volumes at a control site of a chronically infarcted canine ventricle. At the control site, an increase in end-diastolic volume from 31 to 61 ml was associated with an increase in end-systolic volume (from 26 to 46 ml), peak systolic pressure (from 77 to 120 mm Hg), and end-diastolic pressure (from 4 to 32 mm Hg). These hemodynamic changes were associated with a small leftward and parallel shift in the strength-interval relation with the absolute refractory period decreasing by 9 msec (5.1%) in this case. A similar response of refractoriness to volume load at control sites occurred in most hearts. Summary data for the control zone sites are shown in Figure 2. Plotted on the y axis is the coupling interval in milliseconds representing the absolute (Figure 2, Panel A) or relative refractory period (Figure 2, Panel B) for low or high volume loads. Mean absolute refractory period decreased from 178±16.5 to 175±16.7 msec (p<0.05). Although of statistical significance, this small change may or may not be of physiologic importance. The decrease in mean absolute refractory period from 184.2±14.8 to 182.8±16.8 msec was not statistically significant.

The volume-induced changes in refractoriness at infarcted sites were more pronounced. Shown in Figure 3 are the strength-interval relations obtained at low and high volumes from an infarcted site in the same heart as in Figure 1. A similar change in
end-diastolic volume was associated with a much greater, but still parallel, leftward shift in the strength-interval curve at the infarcted site with the absolute refractory period decreasing by 32 msec (21.9%) in this case. Figure 4 contains summary data for infarcted sites. This figure is arranged in the same manner as Figure 2. At low volume, the mean absolute refractory period and relative refractory period were not statistically different from those measured at control sites. With increased volume, however, a significant shortening in absolute and relative refractory periods occurred. The mean absolute refractory period decreased from 171.5±21 to 160.6±26.3 msec (p<0.005), and the mean relative refractory period decreased from 180.1±22.1 to 169.9±26 msec (p=0.05).

The mean change in the absolute refractory periods in the infarcted region was significantly greater than that in the control region (Figure 5). Plotted on the y axis is the difference in absolute refractory periods determined at high and low volumes, and plotted on the x axis is the difference between control and infarcted sites. The change in absolute refractory periods in the infarcted zone was 10.9±10.5 versus 2.6±4.1 msec in the control zone (p<0.05). The difference in the degree of change in relative refractory period was similar (10.1±14 versus 1.4±4.5, p=0.1). This differential effect of volume load on shortening of refractoriness led to an increase in the overall dispersion of refractoriness, as indexed by the coefficient of variance of the absolute refractory period (standard deviation/mean). Increased volume load resulted in an increase in the overall dispersion of refractoriness with the mean coefficient of variance increasing from 6.5±2.1% to 8.4±3.3% (p<0.05).

Pathologic Findings

On gross examination, 13 of 14 hearts showed evidence of infarction. Infarct size, determined by planimetry of four to seven short-axis cross sections, ranged from 0.7% to 18% (6.7±4.4%) of the left ventricle.

Histopathologic examination revealed a gradient of injury from subendocardium to subepicardium with marked heterogeneity of scar pattern from
FIGURE 4. Plots of summary data for refractoriness changes with increased volume at infarcted sites. Panel A, mean absolute refractory periods (msec) at low and high ventricular volumes. Panel B, mean relative refractory periods (msec) at low and high ventricular volumes. Each circle represents the mean value for all runs in a given heart at low or high volume. Each pair of circles connected by a line represents values at low and high volume for a given heart. Squares represent the mean absolute and relative refractory periods for all the hearts at low or high volumes. Significant load-dependent change occurred in both absolute and relative refractory periods in the infarcted region.

FIGURE 5. Plot of summary data of mean change in absolute refractory period with increased volume at control and infarcted sites. Difference in absolute refractory periods with increased volume (msec) is plotted against site type. Change in absolute refractory period with increased volume was greater in the infarcted region than the control regions. \( \Delta \text{ARP} \), change in absolute refractory period.

noted. In 24, confluent scar or patchy fibrosis extended beyond the endocardium into the midmyocardium or epicardium. Transmural, confluent fibrosis was noted in three samples. Control sites showed no evidence of fibrosis.

The particular pattern of scar was associated with the magnitude of load-dependent change in refractoriness at a given site. Figure 6 contains summary data for the 68 sites at which both histopathology and absolute refractory period information were available. Plotted on the y axis is the mean percent change in absolute refractory period obtained at high volume relative to that obtained at low volume. At noninfarcted sites (n = 21), a 2.6 ± 3.7% change in absolute refractory period with load occurred. This magnitude of change in refractoriness also occurred in the tissues exhibiting microfoci of fibrosis (2.2 ± 2.3%, n = 7), scar limited to the endocardium (1.4 ± 1.8%, n = 13), and transmural scar (−1.6 ± 5.0%, n = 3). In contrast, the tissues exhibiting patchy scar extending beyond the endocardium showed a greater change of absolute refractory periods with load (6.1 ± 7.0%, n = 24). The differential response to load of the absolute refractory period change between the groups was significant (p < 0.05 by ANOVA). The only group whose magnitude of change in absolute refractory period with load differed from that noted in the control or noninfarcted myocardium was the group in which patchy scar extended beyond the endocardium. This group showed a heterogeneous response to volume load. At some sites, relatively large changes in refractoriness with load were noted, whereas at other sites, which were indistinguishable pathologically, little or no change was noted.
Effect of Volume Load on Programmed Electrical Stimulation

Eight hearts were noninducible at low volume with programmed electrical stimulation performed at multiple sites (2.8±1.6) with up to double extra stimuli at a drive train cycle length of 350 msec. In these hearts, programmed electrical stimulation was repeated at high volume. Four of the eight hearts were inducible at high volume, two into sustained ventricular tachycardia, and two into ventricular fibrillation. On return to low volume, each of these four hearts returned to a noninducible state, thereby documenting reproducibility. The change in inducibility occurred at two sites in three of the four hearts. Ventricular tachycardia was induced at high volume with a single extra stimulus in one heart and with double extra stimuli in a second heart. Ventricular fibrillation was induced at high volume with a single extra stimulus in one heart and with double extra stimuli in a second heart. At low volume, the mean absolute refractory period was not statistically different at inducible (166±36 msec) and noninducible sites (178±15 msec).

To further evaluate this change in inducibility with volume load and to gain insight into potential mechanisms, we compared the degree of refractoriness shortening at sites showing a change in inducibility with those at sites remaining noninducible. At low volume, programmed electrical stimulation at 24 sites in 11 dogs revealed no inducible tachyarrhythmias. Programmed stimulation at six of these sites resulted in inducible tachyarrhythmias at high volume. There was a significant difference in the degree of shortening of absolute refractory periods (24.6±16.5 vs. 3.9±6.5 msec, \( p < 0.05 \)) and relative refractory periods (41.3±15.5 vs. 5.9±7.3 msec, \( p < 0.001 \)) for sites associated, or not associated, with a change of inducibility of ventricular tachyarrhythmias (Table 2). Thus, load-dependent shortening of refractoriness, which was site specific, led to site specific alterations in inducibility of ventricular tachyarrhythmias.

Discussion

The major finding of this study is that an increase in end-diastolic volume results in greater shortening of refractoriness at infarcted sites than at control sites in ejecting, chronically infarcted, isolated, blood perfused canine hearts. This increased sensitivity to volume load occurs primarily at sites showing patchy scars extending at least to the midmyocardium. In addition, by programmed electrical stimulation, increased ease of inducibility of sustained ventricular arrhythmias with load could be shown in several hearts. Furthermore, this increased ease of inducibility of arrhythmias was associated with the magnitude of change of refractoriness shortening. These findings are consistent with the concept of contraction-excitation feedback, and indicate that volume load may have greater electrophysiologic significance under pathologic conditions.

Contraction-excitation feedback can be defined as the phenomenon whereby changes in mechanics of myocardial contraction precede and result in changes in membrane potential. Contraction-excitation feedback has been studied most extensively in normal myocardial tissue.6-11 In isometrically contracting muscles, moderate changes in length have had little effect on action potential characteristics.10,11,15-17 Marked changes in length, however, have decreased the resting membrane

![Graph](https://example.com/graph.png)

**Figure 6.** Bar graph of summary data for refractoriness changes at different pathologic sites. Percent change in absolute refractory period is plotted on the y axis, and the five pathologic classifications are shown on the x axis. Differences among the groups were significant (\( p < 0.05 \) by ANOVA). Only tissues with scar extending beyond the endocardium had exaggerated shortening of refractoriness relative to noninfarcted myocardium. %ΔARP, % change in absolute refractory period (high compared with low volume).

<table>
<thead>
<tr>
<th>Site Type (status with volume changes)</th>
<th>ΔAbsolute refractory period (msec)</th>
<th>%ΔAbsolute refractory period</th>
<th>ΔRelative refractory period (msec)</th>
<th>%ΔRelative refractory period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remain noninducible</td>
<td>3.9±6.5</td>
<td>2.3±3.7</td>
<td>2.4±7.3</td>
<td>1.1±5.6</td>
</tr>
<tr>
<td>Noninducible to inducible</td>
<td>24.7±16.5</td>
<td>14.9±10.2</td>
<td>41.3±15.5</td>
<td>21.7±5.6</td>
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</table>

Values are mean±SD.
potential and rate of rise of the action potential upstroke. In addition, a change from isometric to isotonic contraction, or a quick release under isometric conditions, was shown in prolonged action potential duration. In the isolated, perfused canine ventricle, an increase in volume under isovolumic conditions has shortened refractoriness and monophasic action potential duration, whereas an acute increase in afterload in the in situ canine ventricle has prolonged refractoriness. Shortening of monophasic action potential duration was shown recently in patients undergoing balloon occlusions of the right ventricular outflow tract. In addition, afterdepolarizations have been reported with increased load in isolated and in situ canine ventricles as well as in patients undergoing balloon valvuloplasty.

The goals of our study were to investigate this phenomenon under pathologic conditions and to assess its possible arrhythmogenic significance with programmed electrical stimulation. Our study was performed in isolated, blood perfused ventricles under steady-state loading conditions. We have shown that there are small volume-dependent changes in refractoriness in normal zones of chronically infarcted ejecting hearts (Figures 1 and 2). The 3-msec mean decrease in absolute refractory period at control sites with increased volume is of a smaller magnitude, though in the same direction as the change in refractoriness reported by Lerman et al in normal isolated canine hearts. This difference in the magnitude of change in refractoriness may have occurred because their study was performed under isovolumic conditions, in a much lower volume and pressure range, and in hearts that showed a lower contractile state.

A differential effect of load on refractoriness in normal and infarcted zones was shown in our study Figures 1–5. Whereas refractoriness shortened by a mean of 3 msec in the control zone, it shortened by a mean of 11 msec in the infarcted region with a volume load. Furthermore, when we classified sites within the infarction zone by the pattern and amount of fibrosis, only sites of patchy infarction extending at least to the midmyocardium showed a greater change in refractoriness than control sites (Figure 6). The mechanism of the association between the magnitude of change in refractoriness and histologic pattern of fibrosis is not known, but can be explained partially by differential changes in local wall stress with load in different histologic subgroups. The similar response to volume load to normal sites located in either endocardial infarcts or infarcts showing only microfoci of fibrosis most likely reflects the small mechanical impact of these infarct types. The absence of large changes in refractoriness in transmural infarcts may reflect the relative protection to stress afforded by transmural fibrosis. Exaggerated shortening of refractoriness with load occurred primarily at sites of patchy infarction and fibrosis extending at least to the midmyocardium.

This may reflect relatively greater local wall stress at high volume at the interface of scar and noninfarcted tissue. The heterogeneous decrease in refractoriness at these sites most likely reflects the importance of electrode proximity to the myocardial and scar interface. These findings extend those of Tobler and colleagues, who studied changes in refractoriness at control and border zone sites induced by transient aortic occlusion in six dogs with chronic infarcts (>14 days old). Their study was limited by the absence of histologic characterization of the infarct or of electrode positions. Furthermore, their study was performed in intact dogs under non–steady-state conditions in which neural influences could not be excluded. Despite differences in the infarction model, in the methods of refractoriness determination, and in the type of hemodynamic intervention, the 17-msec mean decrease in effective refractory period reported in their study at border zone sites compared with little or no change at control sites is consistent with the magnitude and direction of change in absolute refractory periods reported in this study.

Our study showed that an increase in end-diastolic volume resulted in an increased dispersion of refractoriness and an increased incidence of inducible ventricular tachyarrhythmias. Four of eight hearts in which sustained ventricular tachycardia or ventricular fibrillation were not inducible at low volume became inducible at high volume; sustained ventricular tachycardia was induced in two, and ventricular fibrillation was induced in two. When each site at which programmed electrical stimulation was performed was analyzed independently, 25% of sites initially noninducible at low volume became inducible at high volume. This change in inducibility was associated with the magnitude of change in refractoriness; that is, sites at which inducibility changed with load had a greater change in refractoriness than sites without a change of inducibility (Table 2). The increased ease of inducibility of the hearts at high load and the associated increase in dispersion of refractoriness indicates that the differential shortening of refractoriness at infarcted sites relative to control sites may be arrhythmogenic. Although the exact mechanism of increased arrhythmogenesis has not been determined, differential shortening of refractoriness with load may provide the substrate for reentrant tachycardias or focal reexcitation. Differential shortening of refractoriness between adjacent myocardial fibers may lead to functional unidirectional conduction block that is necessary for reentrant tachycardia. Recent studies in canine infarct models provide evidence strongly supporting reentry as the mechanism of ventricular arrhythmias during the early and late postinfarction period. The importance of the magnitude of dispersion and spatial distribution of refractoriness in the development of reentrant rhythms has also been shown.

showed that a refractoriness gradient of 11–16 msec
was sufficient to cause conduction block in isolated atrial strips, and Gough et al.28 showed that conduction block occurred when the difference in effective refractory periods between adjacent sites increased from 10 to 20 msec. Thus, both the magnitude of refractoriness change with load and the heterogeneous response to load observed within the infarcted zone in this study are compatible with the notion that volume load results in the development of an electrophysiologic substrate capable of maintaining reentrant rhythms. Our observation of greater refractoriness shortening with load at sites showing a change in inducibility is consistent with the work of several investigators who have shown that extra stimuli delivered to the sites of shortened refractoriness are most likely to initiate reentrant rhythms.28,30,33 A second potential mechanism for the load-dependent increased arrhythmogenesis is focal reexcitation, which may result from electrotonic current flow between adjacent myocardial fibers with significantly different rates of repolarization.24,34,35

The mechanisms that lead to the differential shortening of refractoriness between infarcted and control zones are unknown. As already noted, a possible mechanism may be related to relative increases in wall stress at border zones of normal myocardium next to scar tissue. This phenomenon, known as “stress amplification,” may result in fourfold increases in local wall stress at the border zone of normal and infarcted myocardium.12 This marked increase in local wall stress at high volume may, in turn, result in some areas of myocardium contracting essentially under isometric conditions. Studies in isolated tissues have shown relative action potential shortening with isometric compared with isotonic contraction18,19 by contraction-excitation feedback. Stretch has also affected the cable properties of Purkinje fibers, which may lead to changes in conduction and refractoriness.36 Thus, differential regional wall stress may have led to the differential shortening of refractoriness we observed.

Although our data are consistent with changes induced by contraction-excitation in refractoriness, we have not proven this, and other mechanisms may also explain the differential change of refractoriness noted. One such mechanism is that myocardium within the infarction zone may have baseline electrophysiologic abnormalities that, in turn, result in a greater sensitivity of electrophysiologic properties to mechanical influences. Although several investigators have shown markedly abnormal transmembrane action potentials during the 1st week after infarction, these action potentials have normalized over time.37,38 By the end of the 2nd week after a two-stage infarction similar to the one in our study, Spear et al.38 found that only the action potential duration at 30% repolarization was significantly different from the control. By studying infarcts approximately 1 month of age, we believe most action potential abnormalities in the early postinfarction period should have resolved, and therefore, we believe, that although possible, this is not a probable mechanism to explain the differential change in refractoriness with load.

A third possible mechanism that explains the differential change of refractoriness is regional ischemia. We believe this is an unlikely mechanism for several reasons. First, although ischemia is associated with shortened refractory periods, reperfusion is associated with rebound prolongation of refractoriness lasting up to 60 minutes after reperfusion.29 In our study, however, rebound prolongation did not occur, and in fact, reproducibility of refractoriness to within 2 msec was required. Second, in another study in which load-dependent changes in refractoriness occurred, ischemia was effectively excluded at high volume by measurement of effluent lactate levels and by showing that the degree of shortening of refractoriness with load was independent of pacing rate.39 Thus, our data are most consistent with changes induced by contraction-excitation feedback. Nevertheless, we have not proven this, and other mechanisms have not been ruled out.

These data may have clinical relevance. Patients with structural heart disease and congestive heart failure have a high mortality related, in part, to a high incidence of sudden cardiac death.1–3 Those patients with elevated wall stress due to an increased end-systolic volume are at particularly high risk.4 Furthermore, one recent study showed that discrete left ventricular dyskinesis may be a more significant predictor of sudden cardiac death than global left ventricular function as indexed by ejection fraction.5 This and the fact that most sustained arrhythmias in patients with prior myocardial infarctions arise in the border zones adjacent to ventricular aneurysms40 supports the notion that increased wall stress at the interface between the aneurysm and normal border zone myocardium may play a role in arrhythmogenesis; that is, arrhythmias develop in those areas most likely to be subjected to the greatest mechanical stress during ventricular systole. Finally, vasodilators in patients with severe congestive heart failure have been associated with a reduction in ambient ventricular ectopy41 and with an improved prognosis that may be related, in part, to a decreased incidence of sudden death.42 Our data support the notion that ventricular volume is of direct electrophysiologic and arrhythmogenic significance in scarred hearts and, therefore, provide one plausible mechanism for the known association between arrhythmias and structurally abnormal, dilated hearts.

In summary, we have shown a differential volume load–dependent shortening of refractoriness between normal and infarcted zones of chronically infarcted canine hearts and an increased ease of inducibility of sustained tachyarrhythmias at high volume. The exaggerated shortening of refractoriness occurs primarily at sites of patchy infarction and fibrosis extending at least to the midmyocardium. Determination of the precise mechanism and clinical rele-
vance of these load-dependent changes will require further investigation.

Acknowledgments

We thank Ken Rent and Rick Tunin for their expert technical assistance and Cheryl Dewyre for typing the manuscript.

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KEY WORDS • heart failure • contraction-excitation feedback • arrhythmia • myocardial infarction
Effect of acute volume load on refractoriness and arrhythmia development in isolated, chronically infarcted canine hearts.
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Circulation. 1989;79:687-697
doi: 10.1161/01.CIR.79.3.687

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