The Relation of Contractile Enhancement to Action Potential Change in Canine Myocardium

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ABSTRACT

Simultaneous recordings of contractile tension and transmembrane potentials from canine ventricular tissue yielded a consistent correlation of action potential (AP) alteration with contractile change associated with abrupt rate change. The AP terminating a relative prolongation of the cycle-length manifested shortening of phase 2 with lengthening of phase 3 and was associated with potentiation of contractile force. Conversely, the AP terminating a relative abbreviation of cycle-length displayed a broader phase 2 with a more precipitous phase 3, while the associated contraction was less forceful than the control. In each circumstance, the relative magnitude of cycle-length change correlated with the extent of both AP change and contractile alteration. Changes in AP configuration may reflect changes in transmembrane flux of K+ during repolarization consistent with the findings of prior workers who have related K+ efflux to increased contractility. Mechanical alternans, in addition, was frequently observed in association with abrupt rate change and was consistently associated with an electrical alternans manifested by action potentials with alternately wide and narrow plateaus (phase 2). As above, the more forceful contractions were associated with action potentials which displayed a narrower phase 2. Mechanical alternans initiated by abrupt rate change may represent an adaptive phenomenon prior to the establishment of a stable contractile state, as reflected by a stable AP configuration.

ADDITIONAL KEY WORDS cardiac repolarization and contractility
cardiac contractility
post-extrasystolic potentiation
compensatory pause and repolarization
mechanical and electrical alternans
rest potentiation
cycle-length, repolarization and contractility

Augmentation of cardiac contraction associated with abrupt rate change has been noted repeatedly in a variety of mammals (1) as well as the human (2) since first described by Langendorff in 1875. The mechanism by which such a phenomenon occurs has, nevertheless, remained obscure and of little more than academic concern until recently. With the advent of implanted artificial pacemakers, however, it has become apparent that exploitation of this apparently intrinsic myocardial property may be of considerable utility in the treatment of cardiac dysfunction. Paired pulses, e.g., producing sustained post-extrasystolic potentiation, appear capable of enhancing cardiac function to a substantial degree (2).

Observed under a variety of circumstances (in the post-extrasystolic contraction, in the first beat at a slow rate following a rapid rate, and in the first contraction following a period of quiescence), such potentiation has been attributed to an effect of the premature beat per se (3), to increased diastolic filling...
associated with the compensatory pause, or to an imbalance of positive and negative inotropic substances (4) engendered by each excitation. This augmentation of contraction need not be associated with diastolic filling alone, as potentiation has been demonstrated in vitro (1) without change in resting fiber length.

A fundamental interval-strength relation, common to all varieties of potentiation produced by abrupt rate change, has been observed in several studies (4, 5); it is constituted by the relative prolongation of the cycle-length (i.e., prolongation relative to the previous cycle-length) preceding the potentiated contraction. The physiologic mechanism of such enhancement has not been further clarified, however.

Most studies (1, 3, 6, 7) of these inotropic (8) phenomena have suggested, nevertheless, that interval-dependent potentiation is mediated through changes in excitation-contraction coupling and is not associated with alteration in the excitatory process itself. Action potential (AP) changes, concomitant with increased contraction, have either not been demonstrated or have been construed as of no significance; neither the AP duration nor its amplitude have been found to increase with augmentation of contractility. Earlier studies in this laboratory(9)2 have, however, demonstrated a characteristic AP change following a sudden prolongation of the cycle-length. This report documents a temporal relation between altered AP configuration and enhancement of myocardial contractility which suggests that potentiation of contractile force may indeed be contingent upon, or related to, changes in membrane excitation or recovery.

**Method**

Ten adult dogs, varying in weight from 10 to 15 kg, were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Following a mid-sternal incision, the heart was removed and immediately placed in oxygenated Tyrode solution. Papillary and trabecular muscles (0.5 to 1.0 mm diam) were isolated from the right ventricle and immersed in a 30-ml chamber perfused with oxygenated Tyrode solution. One cut end of the muscle was clamped to a plastic block by coated steel watch springs. The other end was impaled by a steel hook suspended from a gold chain, which in turn was connected to a Statham Universal Transducing Cell (Model UC3). Tension was recorded via an 8 trace switched-beam oscilloscope (Electronics for Medicine) and records were photographed on 7-inch paper moving at a speed of 100 mm/sec. Transmembrane potentials were recorded simultaneously on the Electronics for Medicine recorder using an intracellular microelectrode (9). Driving and premature stimuli, as previously described (9), were administered by bipolar stainless steel wire electrodes (0.005-inch diam).

**Results**

Contractile tension and action potentials were recorded simultaneously from ventricular tissue in a variety of circumstances. AP configuration was unaltered while the contractile force exhibited remained undiminished over a period of 2 to 4 hours. With a basic stimulus rate varying from 40 to 120/min, changes in cycle-length were introduced by stimuli of variable prematurity and by quiescent periods of variable duration. From ventricular myocardium of each animal, 50-75 sequences were recorded. Representative examples of each type of rate change are discussed below (there were no deviations from the patterns to be described).

**PO5T-EXTRASYSTOLIC POTENTIATION, EXTRASYSTOLIC DEPRESSION OF CONTRACTILE FORCE**

Figure 1 demonstrates recordings of tension and action potentials following "extrasystoles" (marked by arrows) of varying prematurity. In each case, the premature contraction (following interval b which is shorter than the dominant cycle-length, interval c) exhibits a weakened contraction and is associated with an AP that displays a longer phase 2 and a more precipitous phase 3 than the control AP. In contrast, Figure 2 shows post-extrasystolic contractions (following interval

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1. The term inotropy in this text refers to the force-velocity relation of myocardial tissue as described by Sonnenblick.
Action potentials (AP) and contractile tension (t) associated with "extrasystoles" (marked by arrows) were initiated at different intervals after the regularly stimulated events (labeled $t_1$ and $t_2$). The dominant cycle-length is labeled c. In panels A, B, C, the premature AP and developed tension (labeled 2 and $t_2$) follow intervals (labeled b) which are shorter than interval c. In each case, the premature AP exhibits a longer phase 2 and is associated with a weakened contraction. In panel A, the premature stimulus follows the shortest cycle-length with respect to interval c and elicits the weakest contraction and an AP with the longest phase 2. In panel C, the premature stimulus follows the longest interval (i.e., it is the least premature stimulus) and the associated AP exhibits the least phase 2 widening and is accompanied by the most forceful of the premature contractions. In panel B, the stimulus is of intermediate prematurity, associated with a contraction of intermediate strength and an AP with a phase 2 of intermediate length. The AP differences are illustrated by superimposition in the lower right panel; the configurations of the action potentials marked 1 in A, B, and C are identical.

Examination of the records (Figs. 1 and 2) discloses further that the extent of change, in both the AP and contractile tension, bears a relation to the magnitude of change in the duration of the immediately preceding cycle-length. In other words, a more marked shortening of the cycle-length (a smaller ratio, interval b/interval c) is associated both with a longer phase 2 of the AP and with a less forceful contraction. Conversely, a greater prolongation of the cycle-length (i.e., an increased magnitude of the ratio, interval a/interval b)
Postextrasystolic beats exhibited a more forceful contraction when preceded by an early premature contraction. The associated action potentials show an abbreviated phase 2 and prolonged phase 3. In each panel, the postextrasystolic beat occurs after a cycle-length that is prolonged relative to the preceding interval (interval a is greater than interval b). In panel B, both a more forceful contraction and an AP with a shorter phase 2 are associated with a greater prolongation of the cycle-length (i.e., a greater ratio of interval a/interval b). This should be compared with Figure 1 in which a smaller ratio (interval b/interval c) is associated with a wider phase 2 of the AP and with a less forceful contraction. Superimposition of the action potentials is shown at the right of each tracing.

Late Interpolated Extrasystoles

Figure 3 illustrates the effect of extrasystoles which are interpolated late in diastole. In these instances, the second contraction after the extrasystole (i.e., following interval a, the basic stimulus interval) exhibits contractile potentiation as well as distinct phase 2 shortening of the accompanying action potential. The first contraction after these extrasystoles (i.e., following interval b), in contrast, is not enhanced with respect to the control contraction. This indicates that marked potentiation is not conferred upon the postextrasystolic beat by the premature contraction per se, but that such augmentation occurs only after a relative prolongation of the cycle-length. Figure 3 also shows a direct relation between the degree of cycle-length prolongation (i.e., the magnitude of interval a/interval b) and the extent of contractile and action potential change (see Table 1). In other words, a greater contractile augmentation, proportionate to the control contraction, is associated with a more pronounced change in the action...
Tracings A and B illustrate extrasystoles (marked by arrow) interpolated late in diastole. In such cases it is the second beat (following interval a) after the extrasystole which shows contractile potentiation ($t_1$) and phase 2 abbreviation (AP#2). This is further illustrated by superimposition of the action potentials at the right of each tracing. The first contraction and AP (after interval b) following the extrasystole, in contrast, is not enhanced with respect to the control (AP#1, and $t_1$). See text for explanation. Again, there is a relation between the extent of contractile and AP change and the magnitude of interval a/interval b.

### Table 1

<table>
<thead>
<tr>
<th>Figure</th>
<th>Type of contractile change</th>
<th>Contractile change (% of control)</th>
<th>Cycle-length change*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Extrasystolic depression</td>
<td>A 25.0 B 30.4 C 73.3</td>
<td>(b/c)</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>Post-extrasystolic potentiation</td>
<td>A 229.0 B 300.0</td>
<td>(a/b)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>Post-extrasystolic potentiation</td>
<td>A 214.0 B 470.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Rest potentiation</td>
<td>A 133.0 B 150.0</td>
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*Length of cycle-length preceding contraction, expressed as percent of prior cycle-length.

potential configuration and both such changes correlate with the relative extent of cycle-length prolongation. The AP changes are again illustrated by superimposition at the right of each recording.

Comparison of Figures 2 and 3 reveals a
lack of close correspondence between the magnitude of contractile augmentation and the relative degree of cycle-length alteration. Nevertheless, in each circumstance, prolongation of the cycle-length yields successively greater contractile responses associated with more prominent AP alteration.

**REST POTENTIATION**

Figure 4 demonstrates recordings interrupted by omission (interval a) of a variable number of stimuli. Here, the first contraction following the rest period is potentiated and associated with an AP that bears a shortened phase 2 and a lengthened phase 3, without change in AP duration. Also revealed by this figure is a direct relation between the duration of rest (the magnitude of interval a/b) and the degree of both contractile enhancement (see Table 1) and AP change. These changes are again illustrated by superimposition at the right of each tracing.

It may be observed that the extent of contractile augmentation, proportionate to the relative magnitude of cycle-length prolongation, is less with rest potentiation than following a premature extrasystole (see Table 1). By the same token, it may also be noted that the degree of AP alteration, relative to a similar degree of cycle-length prolongation, is less in rest potentiation than in post-extrasystolic potentiation.

**MECHANICAL ALTERNANS**

Figure 5 illustrates mechanical and electrical alternans associated with a more rapid stimulus rate (75/min). The more forceful contractions are associated with an AP displaying a less prominent phase 2, although AP duration remains unchanged. This relationship is illustrated clearly by superimposition of the action potentials at the right end of the figure. There is no difference in the duration of contraction of the less forceful and more forceful beats; in each case, the time-to-peak tension remains constant. Thus, the more forceful contractions are characterized by a more rapid rate of force development, reflecting a more rapid rate of contractile shortening. The same phenomenon, one of potentia-
tions consequent to an increased velocity of contraction, may be observed in Figures 2 through 4 (a characteristic of post-extrasystolic potentiation as noted by other investigators) (1, 10).

**Discussion**

These studies reveal characteristic alterations in canine ventricular AP configuration associated with interval-dependent changes in contractile tension. Following a relative prolongation of the cycle-length both shortening of phase 2 of the AP and potentiation of contractility are observed. In contrast, a relative abbreviation of cycle-length is associated with both depression of contractility and widening of phase 2 of the AP. These interval-dependent alterations in contractility are reflected by post-extrasystolic, post-stimulation and rest potentiation, as well as by depression of contractility associated with a premature stimulus. It has also been observed that in each circumstance the extent of AP alteration correlates with the magnitude of contractile change and that both phenomena appear to be a function of the relative degree of cycle-length alteration. Thus, a more premature contraction is associated with both a less forceful contraction and an AP that bears a wider phase 2; the ensuing post-extrasystolic stimulus, terminating a cycle-length that is more prolonged relative to the preceding interval, evokes an even greater degree of contractile enhancement and is associated with an AP displaying a shorter phase 2. These changes are consistent and predictable, occurring under all conditions tested, and they appear to be more directly related to the relative degree of cycle-length alteration than to the absolute length of any single interval.

**REST POTENTIATION**

As described by others (4, 11), rest potentiation of contractility is considerably less prominent than post-extrasystolic or post-stimulation potentiation, relative to the magnitude of cycle-length prolongation. Thus, a sixfold prolongation of cycle-length, by stimulus omission, yielded a 56% greater contraction (see Fig. 4B); while only a little more than threefold prolongation of the interval, following a premature stimulus, was terminated by a contractile force that was 370% greater than the control (see Fig. 3B). Several observers, in order to explain the vagaries of such interval-dependent contractile phenomena, have invoked the presence of positive and negative inotropic factors (4) or potentiating substances (12) engendered by each contraction and decaying exponentially with time. Presumably, the imbalance of such forces determines the extent and direction of contractile change following cycle-length alterations; while the persistence of a low-activity positive inotropic factor gives rise to a rest potentiation of lesser amplitude than the post-extrasystolic potentiation.

Although the current study does not offer
further insight into this disparity between rest potentiation and post-extrasystolic potentiation, it does suggest a more fundamental characteristic of such interval-dependent inotropic phenomena. While the contractile augmentation of rest potentiation was indeed less marked (proportionate to the interval prolongation) than that of post-extrasystolic potentiation, the extent of AP change associated with rest potentiation was also less prominent. A three-fold prolongation of the cycle-length in post-extrasystolic potentiation produced a much more striking abbreviation of phase 2 than that observed in the post-rest AP, following a sixfold prolongation of the cycle-length. Thus, the magnitude of contractile potentiation appears more closely related to the extent of AP alteration than to the degree of interval prolongation per se.

Physiologic Considerations

Most prior studies have concluded that these types of inotropic phenomena are not accompanied by discernible alterations in the excitation process itself (4, 6, 11) (i.e., AP changes). Such a conclusion appears based on the well documented observation (13) that protracted depolarization (i.e., a wider AP) is associated with a more vigorous contraction, presumably via prolongation of the active state or the recruitment of greater numbers of myocardial fibers. As noted by Vaughn Williams (13) and Niedergerke (14), however, prolongation of the AP is hardly sine qua non for the potentiation of contractile force. Studies of guinea-pig atria (7) demonstrate AP changes, in association with rest potentiation, that are quite comparable to those observed in canine ventricular tissue; that is, acceleration of early repolarization (shortening of phase 2) and slowing of terminal repolarization (lengthening of phase 3) are observed in association with contractile augmentation. These latter investigators also question the likelihood of a causal relation between such AP changes and contractility, noting that the altered repolarization follows the initiation of contraction. They do not, however, consider the more plausible thesis that such AP alteration need not initiate contractile change, but that both AP and contractile change may reflect an alteration in ionic flux or permeability that is conducive to contractile potentiation. In any case, it does not seem reasonable to assume that an AP change, unless of altered duration, cannot be directly implicated in alteration of contractility.

Recent studies by Langer and Brady (15), moreover, suggest that time-dependent alteration in the flux of sodium, calcium, and potassium ions may be intimately related to variation in the speed and extent of contraction. Ostensibly, nonionic calcium sequestered in intracellular vesicles augments contraction when made available at the contractile site. But for the latter to occur, these calcium ions must compete with sodium ions, which in turn must be actively extruded from the cell in order to maintain ionic equilibrium. Active transport of sodium is not sufficiently responsive to effect such an immediate transfer, however, and the demands of ionic equilibrium are met by rapid efflux of potassium ions. The studies of Langer and Brady (15), as well as Hajdu (16), are consonant with such a hypothesis, demonstrating K+ efflux in association with positive inotropic responses. Moreover, Samoff et al. (17, 18) have recently observed an association between augmentation of contractility and a net loss of K+ from the isolated canine heart. Our studies are also in accord with the above hypothesis, demonstrating post-extrasystolic action potential changes which are quite consistent with increased K+ efflux. These data suggest also that the converse may be true, i.e., that decreased K+ efflux during repolarization (reflected by phase 2 widening) is associated with depression of contractility. Implied in this discussion, needless to say, is the assumption that these AP changes may be initiated by other types of ionic flux. The primacy of K+ is invoked here only because it is compatible with the experimental observations of others (15-18) and because repolarization is generally conceived to be generated by the efflux of K+ ions.

As previously described, other studies (1,
10) have characterized post-extrasystolic potentiation as a manifestation of altered contractility, since this type of contractile potentiation exhibits more rapid force development without change in resting fiber length. Our studies suggest, furthermore, that all interval dependent alterations in contractile force reflect an inotropic intervention; each of these contractile changes (depression as well as augmentation) is associated with an alteration in the rate of force development without change in time-to-peak force development. These findings also suggest that such inotropic changes associated with characteristic action potential alterations may be mediated through variation in K+ flux or membrane permeability to K+.

MECHANICAL AND ELECTRICAL ALTERNANS

As described, mechanical alternans was characteristically observed for a variable period following a period of quiescence, or after an abrupt and marked acceleration of rate. Comparable data have been presented by Nayler and Robertson (6), who described "two groups of contractions" following a period of quiescence, one displaying a negative treppe or "staircase," the other exhibiting a positive staircase. In other words, the first, third, and fifth, etc., contractions presented a progressive decline in contractile tension; while the second, fourth, sixth, etc., contractions manifested a progressive increase in the force of contraction. These investigators (6) described no concomitant change in transmembrane potentials, however, concluding that "this pattern of contractile behavior does not reflect an altered state of electrical excitation." Again, these investigators considered only the magnitude and duration of the action potentials as of pertinence. Our studies, in contrast, show a cyclic alteration in AP configuration, associated with the mechanical alternans. And as in the case of the weak extrasystolic contraction and the potentiated post-extrasystolic contraction, the magnitude of contractile force appears inversely related to the length of phase 2.

No variation in end-diastolic tension was noted in association with the mechanical alternans observed here. Instead, the more forceful contractions were associated with more rapid force development, without change in time-to-peak force development. Other investigators (19) have, however, described mechanical alternans as a function of alternating end-diastolic fiber lengths. Such disparate observations suggest that mechanical alternans may occur in a variety of metabolic and physiologic states. It has been demonstrated, nevertheless, that other types of contractile enhancement associated with characteristic AP alterations are contingent upon an altered force-velocity relation independent of change in end-diastolic fiber length. For example, post-extrasystolic potentiation has been observed in vitro (1), where increased diastolic filling is no longer a factor. Thus, it appears reasonable to suggest that the mechanical alternans associated with similar alternation of AP configuration may reflect a primary alternation of force-velocity characteristics without changes in end-diastolic fiber length. This type of mechanical alternans is characteristically initiated by abrupt rate change and may represent an adaptive phenomenon prior to the establishment of stability (with respect to both mechanical and electrical properties).

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