Effect of Cycle-Length Alteration upon the Configuration of the Canine Ventricular Action Potential

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ABSTRACT

Action potentials recorded from canine ventricular fibers displayed characteristic alterations in configuration upon abrupt change in the cycle length. After a relative prolongation of the diastolic interval, abbreviation of phase 2 and slowing of phase 3 were consistently observed, while a relative shortening of diastole was terminated by an action potential displaying prolongation of phase 2 and a steeper phase 3. Neither circumstance was attended by a consistent alteration in action potential duration. The more conventional view, directly relating duration of phase 2 to the length of the preceding diastole, clearly does not obtain immediately following an abrupt alteration of cycle length.

This cycle-length-dependent phenomenon may account, in part, for the postextrasystolic T-wave alterations observed in the human electrocardiogram. It is also consistent with the clinical observation that such T-wave changes may occur without premature contractions, requiring only a relative prolongation of the R-R interval. Evidence is also presented which relates electrical alternans of the T wave to this interval-dependent phenomenon.

This characteristic change in action potential configuration occurs under the same temporal circumstances that others have associated with potentiation of contractility. It is therefore suggested that these inotropic phenomena and changes in action potential configuration may relate to alterations in membrane permeability.

ADDITIONAL KEY WORDS

- action potential duration
- cycle length and repolarization
- compensatory pause
- interpolated action potential
- Q-T interval
- electrical alternans
- potentiation of contractility
- cardiac membrane permeability

A direct relation has been previously noted between the electrocardiographic Q-T interval and the preceding R-R interval: the Q-T interval is greater at slower rates and following a longer diastolic interval. The electrophysiologic corollary, that of a direct relation between the duration of the ventricular action potential and the preceding cycle length, has also been observed. Specifically, phase 2 of the action potential is the principal variable, while phase 3 is relatively fixed in slope and duration. Thus, phase 2 is prolonged at slow rates, and shortened at rapid rates. These observations are demonstrably valid at regular stimulus intervals.

The direct relation of the length of phase 2 to the preceding diastolic interval appears less certain in the event of abrupt cycle-length change, however. Hoffman et al. have, in fact, demonstrated phase 2 abbreviation of the canine ventricular action potential terminating a compensatory pause after a premature com-
plex. The premature complex, moreover, following a shorter diastolic interval, displays prolongation of phase 2. These action potential alterations are not associated with significant changes in action potential duration, owing to a reciprocal relation between phase 2 and phase 3 durations. An abbreviated phase 2 is thus followed by a longer phase 3; while a more sustained phase 2 is followed by a shorter precipitous phase 3. Studies in this laboratory have confirmed these latter observations. Accordingly, an investigation was undertaken to clarify the relation of abrupt rate change to action potential configuration.

**Methods**

Adult dogs varying in weight from 10 to 15 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Following a midsternal incision, the heart was removed and immediately placed in oxygenated Tyrode solution. Strips of right ventricular myocardium (1.0 X 2.5 cm), grossly free of Purkinje fibers, were excised immediately, placed in a 20-cc muscle chamber, and continuously perfused with oxygenated Tyrode solution. Both endocardial and epicardial surfaces were employed for electrophysiologic study, although not simultaneously and rarely in the same specimen.

The Tyrode solution, in millimoles per liter, was composed of NaCl, 137.0; KCl, 2.7; MgCl, 0.5; NaH₂PO₄, 0.18; NaHCO₃, 12.0; glucose, 5.5; and CaCl₂, 2.7. This solution, aerated with 95% oxygen and 5% CO₂, was continuously infused at a rate of 60 drops per min. The temperature of the solution entering the tissue chamber was maintained constant at 37°C (± 1°) and the fluid level was maintained by constant overflow suction.

Microelectrodes having a tip diameter about 0.5 μ were drawn from 1 mm glass capillary tubing and filled with 3 M KCl. The electrode resistance was measured using 20 to 60 megohms as the standard of acceptability. A modified Brinkman micromanipulator was used to place the electrode and impale single cells. The microelectrodes were coupled to the input of a Bioelectric Instruments Inc. Model 15A-100, stimulus isolator. Two synchronized stimulus generators were used to introduce stimuli of variable prematurity; extrasystoles could be introduced by switching from one generator to the other.

**Results**

The present study discloses a characteristic pattern of ventricular fiber action potential change, associated with abrupt cycle-length alterations. The cycle-length change was produced in a variety of ways: (1) a premature action potential followed by a compensatory pause; (2) an interpolated action potential; and (3) a stimulus omission for a variable interval. Following a relative prolongation of the diastolic interval (i.e., an interval that is longer than the immediately preceding diastolic interval), there occurs an abbreviation of phase 2, with a decrease in the slope of phase 3. Conversely, the action potential that terminates a relatively short diastolic interval (i.e., an interval shorter than the immediately preceding diastolic period) reveals a sustained phase 2 and a more precipitous phase 3. These phenomena are illustrated in Figures 1 through 5.

Figure 1 demonstrates several series of ventricular fiber action potentials, with premature action potentials followed by compensatory pauses. As can be readily observed, the action potential following the pause (interval “a,” a...
Premature action potentials, with compensatory pauses. A is recorded from endocardium; B is from an epicardial fiber. The premature action potential in each tracing is marked by an arrow. Note the abbreviation of phase 2 following the compensatory pause (interval "a" greater than interval "b"). In B, the premature action potential (following interval "b", relatively shortened) clearly demonstrates prolongation of phase 2. In this and subsequent tracings, the time pulse below the action potential recordings is 100 msec in duration and 15 mv in amplitude. At the far right of strips A and B, action potentials 1 and 2 are superimposed, illustrating the altered configuration after the relative pause.

**Figure 1**

relative lengthening of the diastolic interval) consistently manifests a shortened phase 2 followed by a prolonged phase 3 with a lessened slope. The total action potential duration and amplitude remains essentially unchanged, however. The premature action potential, following a relatively short diastolic interval (interval "b") frequently reveals a more prolonged phase 2, with a steeper, shortened phase 3. As before, the total action potential duration remains unchanged. The above alterations are comparable to those described in previous investigations regarding extrasystolic and post-extrasystolic action potential changes.

Figure 2 shows action potentials interpolated in a series of regularly stimulated action potentials. These interpolations (marked by arrows) are initiated either midway or late in the dominant cycle. In contrast to the example seen in Figure 1, it is the second action potential after the premature complex that exhibits shortening of phase 2, as this complex follows a relatively prolonged diastolic interval (interval "a"). The converse is noted in regard to the interpolated action potential (marked by arrows) which usually demonstrates a more sustained phase 2; this action potential terminates a relatively short diastolic interval (interval "c").

Figure 3 also illustrates interpolated action potentials, but these are initiated early in the dominant cycle. In this case, the first action potential following the interpolated complex manifests shortening of phase 2. This latter change, as before, follows a relatively long distolic interval (interval "a"), conforming to the previously described pattern of action potential alteration relative to changes in cycle-length. The interpolated action potentials, although following a relatively short diastolic interval (interval "b"), do not consistently display prolongation of phase 2, however. Again, action potential duration is not increased following a relative pause; Figures 3A and B actually show a slight shortening of the complex following a relative prolongation of the diastolic interval.

Figure 4 exhibits a series of regularly spaced action potentials initiated after a 30-sec to 3-min period of quiescence. The initial action potential, following the quiescent period, is
Late interpolated action potentials. A is record from endocardium; B is from epicardium. These interpolated action potentials (arrows) do not interrupt the regular sequence, occurring midway or relatively late in their respective cycles. In trace B, the interpolated action potential (following interval "c" which is shorter than interval "d") shows prolongation of phase 2. The second action potential, following the interpolation, exhibits abbreviation of phase 2 (occurring after a relatively long pause; interval "a" is greater than interval "b"). The difference between action potentials 1 and 2 is illustrated by superimposition at the right (it should be emphasized that interval "a" of each trace is equal to interval "d").

Early interpolated action potentials. A and B are recorded from endocardium. The interpolated action potentials (arrows) are initiated early in their respective cycles. In each tracing, the action potential following the interpolated beat manifests phase 2 attenuation (pause "a" is long in relation to the preceding interval "b"). The premature action potential in trace A (terminating "b", less than "c") exhibits prolongation of phase 2. The differences between action potentials 1 and 2 are illustrated by superimposition at the right of each trace.

Characterized by marked abbreviation of phase 2, prolongation of phase 3, and occasional shortening of the total action potential duration (although the duration usually remains unchanged) relative to subsequent action potentials. In contrast, the second action potential after the pause manifests a marked prolongation of phase 2, with a more precipitous phase 3. This sequence is also in conformity with the established pattern. The first action potential (marked by arrows) occurs after a lengthy pause (interval "a") which is prolonged in relation to the last diastolic interval preceding quiescence. The second action potential follows a diastolic interval that is markedly shortened (interval "b") relative to the quiescent period. Following the first two action potentials, an electrical
alternans of variable duration occurs with progressively decreasing variation in action potential configuration, prior to the establishment of a stable, repetitive action potential (see below).

This last group of observations, which were demonstrated repeatedly and consistently, appears in diametric opposition to the observations of Hoffman and Cranefield. These authors have reported that the action potential terminating a long pause is prolonged, with a wide phase 2. Although this apparent contradiction cannot be readily resolved, it is to be noted that the current observations adhere to a consistent pattern of time-dependent action potential changes. Furthermore, continuous recordings as shown in Figure 5, including a quiescent period of variable duration, regularly exhibit phase 2 abbreviation of the first action potential following such a quiescent interval (interval "a", a "relative lengthening" of the diastolic period). This is also succeeded by a series of cyclic alternation in action potential configuration.
ELECTRICAL ALTERNANS

Electrical alternans of ventricular repolarization, as illustrated in Figures 4 and 6, was frequently observed with rate changes. As described by Lepeschkin for the T wave of the electrogram, and by Hoffman and Suckling regarding the basic action potential, this was more commonly associated with an abrupt acceleration of rate. As further noted by the latter authors, this type of alternans consisted of shortening of phase 2 and a decrease of phase 3 slope on alternate action potentials. The variation of the alternans, while occurring without cycle-length changes, appears morphologically comparable to the alternate configuration of premature and post-extrasystolic action potentials. Thus, the findings of this study are consistent with the observation that electrical alternans of repolarization is a function of abrupt rate change.

It may also be noted that the alternans is not necessarily initiated in the manner proposed by Lepeschkin. The latter author has hypothesized that alternans is evoked by an abrupt increase in stimulus rate, resulting in a narrowing of the first Q-T interval (or the first action potential) that follows a brief diastolic interval. Subsequent action potentials, stimulated at a constant but rapid rate, follow alternately long and short diastolic intervals as a consequence. According to this hypothesis, wide and narrow action potentials result from, respectively, long and short diastolic intervals. As illustrated in Figure 6, however, it may be readily observed that the action potential terminating the first brief diastolic interval (a relatively short diastolic interval) of the more rapid rate, characteristically exhibits a prominent widening of phase 2. The ensuing alternans frequently displays no variation in action potential duration or diastolic interval. Where the electrical alternans is constituted by alternately wide and narrow action potentials, the duration of the complexes does indeed vary with the duration of the preceding diastolic interval; yet, in every case, the initial, abbreviated diastolic interval is terminated by a wide action poten-

FIGURE 6

Trace A, recorded from epicardial cells, illustrates electrical alternans produced following an abrupt acceleration in rate. The diastolic interval is unchanging between action potentials of different configuration (see superimposed action potentials labeled A). The first action potential of the alternans (marked by arrow) terminating a relatively brief diastolic interval, displays a more prolonged plateau as compared to the preceding action potential. Trace B, recorded from endocardial cells, illustrates electrical alternans produced by the initiation of activity after a period of quiescence. Here, however, a slight variation of the diastolic interval is present. The wider action potentials with a more prominent plateau follow the longer diastolic interval (see superimposed action potentials labeled B).
tial with a long phase 2. Subsequent stimuli occur at fixed intervals; therefore, with alternately wide and narrow action potentials, it is apparent that wider complexes must follow longer diastolic intervals (i.e., a casual relationship need not be invoked).

EPICARDIUM AND ENDOCARDIUM

A difference between epicardial and endocardial action potentials was noted in the present study, as illustrated in Figures 1 through 5. The epicardial complexes are uniformly of shorter duration and frequently of less amplitude than the endocardial complexes. This observation is consistent with the studies of Moore et al. who recorded action potentials simultaneously from epicardial and endocardial surfaces. Such a disparity between the rates of repolarization is thought to explain the approximate concordance of the T and QRS vectors in the clinical electrocardiogram, producing upright T waves in the presence of tall R waves.

No attempt is made here to construct an electrogram from epicardial and endocardial action potentials, however. For such a graphic reconstruction, to determine the type of T-wave change resulting from altered repolarization, is apt to yield spurious electrograms. Endocardial and epicardial activity were recorded neither simultaneously nor in the same specimen, and only occasionally in the same animal.

Discussion

These studies demonstrate a characteristic change in action potential associated with abrupt alteration of rate. Following a relative prolongation of the diastolic interval, abbreviation of phase 2 is noted. Similarly, the action potential terminating a relatively brief cycle length generally, but not consistently, displays a prolongation of phase 2. These phenomena were observed in a variety of circumstances and, as noted, appear unrelated to premature contractions per se or to the absolute duration of the preceding diastolic interval. It was also observed that the action potential terminating a relative alteration in cycle length does not vary significantly in duration from that of the dominant action potentials. This is attributable to a reciprocal relation between the duration of phase 2 and phase 3, following a relative change in cycle length. Phase 2 abbreviation on the one hand, is followed by lengthening of phase 3, while prolongation of phase 2 is terminated by a precipitous, brief phase 3.

These observations reveal that the traditional concept of a direct relation between duration of phase 2 and preceding cycle length obtains only at regular stimulus rates.

The physiologic mechanism whereby repolarization is altered by cycle-length change remains obscure, as does the nature of repolarization itself. However, assuming that the configuration of the action potential is a function of cyclic variation in potassium (K) and sodium (Na) permeabilities (P), one may speculate that either a regenerative increase in P_K or enhanced K efflux may occur earlier following a relatively long diastolic interval. A relatively short diastolic interval, on the other hand, may effect a delay in the initiation of K efflux. The reciprocal relation between the duration of phase 2 and the slope of phase 3, as noted by Hoffman and Suckling regarding post-extrasystolic changes, may thus be related to changes in the regeneration of K permeability. An abbreviated phase 2 plateau, under this circumstance, is associated with a more gradual, prolonged phase 3. Conversely, a sustained phase 2 plateau is followed by a more precipitous phase 3, of shorter duration.

ECG IMPLICATIONS

These rate-dependent action potential changes, in canine ventricular tissue, may provide an explanation for certain electrocardiographic phenomena in humans. T-wave alterations (changes in magnitude, contour or polarity) have been observed commonly in humans following abrupt alteration of rate. And, while usually referred to as a post-extrasystolic T change, this phenomenon has been observed in the absence of a premature contraction, (e.g., after a pause produced by a nonconducted atrial premature contraction). Thus, what appear to be primary T-wave
changes characteristically occur after a relatively prolonged R-R interval. These ECG alterations may be dependent upon rate change alone, therefore, and unrelated to metabolic changes associated with the increased diastolic filling interval or to the compensatory pause itself. Hoffman and Suckling have, in fact, demonstrated a shortening of phase 2 of the canine ventricular action potential following a premature action potential and compensatory pause. Moreover, the action potential alteration was associated with an altered T-wave configuration in a simultaneous ventricular electrogram.

Our findings do not explain the clinical observation that post-extrasystolic T-wave changes are more commonly associated with overt cardiac disease. However, one may speculate that noxious factors such as ischemia or digitalis, which are known to affect primary T-wave changes through "local differences in the duration of the excited state" may locally potentiate rate-dependent changes in repolarization. In this manner, with disproportionate affection of endocardial or epicardial action potentials by abrupt cycle-length change, alteration in T-wave polarity as well as magnitude may be elicited following an extrasystolic complex.

The infrequency of post-extrasystolic T-wave change, in individuals with normal hearts, is less readily reconciled with our observations from canine ventricular tissue. One would normally anticipate a T wave of lesser magnitude in the post-extrasystolic complex, due to the decreased phase 3 slope, as Hoffman and Suckling have demonstrated a direct relation between T wave amplitude and the rate of voltage change across the membrane during phase 3. On the other hand, with no change in the relative duration of epicardial and endocardial activity, and with repolarization altered proportionately in both endocardium and epicardium, a change in polarity seems less likely. These post-extrasystolic alterations may be of insufficient magnitude to be recorded in the surface ECG of normal hearts, however.

It is of interest that these cycle-length-dependent alterations in action potentials are not generally associated with changes in action potential duration. It has also been observed that post-extrasystolic T wave alterations are infrequently associated with changes in the Q-T interval. The latter observation is consistent with the findings of this study; since post-extrasystolic Q-T prolongation would occur consistently if phase 2, and, hence, action potential duration were always to vary directly with the preceding diastolic interval.

**Electrical Alternans**

The phenomenon of electrical alternans of the action potential in canine ventricular fibers appears to be similarly related to abrupt changes in cycle length. As observed in this laboratory, as well as by Hoffman and Suckling, there is a striking morphologic similarity between the changes noted in premature and post-extrasystolic action potentials and those seen in electrical alternans. In addition, electrical alternans is initiated by an abrupt abbreviation of diastolic length. The shortened diastolic interval is terminated by an action potential that exhibits a wide phase 2, with or without widening of the total action potential. This latter observation conflicts with the postulations of Lepeschkin, who suggests that "cardiac activity" is shortened following an abbreviated diastolic interval. This hypothesis relates electrical alternans of the action potential (i.e., alteration of repolarization) to the conventional theory of action potential duration, in which the duration of the complex is directly related to the length of the preceding diastolic interval. Observations in this laboratory suggest, instead, that electrical alternans of the action potential is a function of prolongation of phase 2 following an abrupt shortening of cycle length. The ensuing alternans, often transient as noted by Lepeschkin, may represent an adaptive phenomenon prior to the establishment of a stable action potential.

**Contractility Potentiation and Action Potential Configuration**

One may also speculate concerning a possible relation between action potential con-
figuration and changes in contractility. Post-extrasystolic potentiation of contractility has, for example, been observed in both the dog and the human. Post-stimulation and rest potentiation have also been described in a variety of animals. In each instance, the force of contraction has been augmented following a relative prolongation of the diastolic interval. Moreover, action potentials recorded by Hoffman et al. (concurrently with measurements of contraction) display shortening of phase 2 after the compensatory pause and in association with enhancement of contractility. Most prior studies have, nevertheless, concluded that action potential change does not correlate significantly with this potentiation of contractile force. This conclusion is based, in part, on the absence of significant changes in action potential duration associated with potentiated beats; other studies suggest that in different circumstances action potential duration relates directly to increased contractile tension. In any case, our study finds no consistent change in action potential duration following prolongation of the diastolic interval. A characteristic change in action potential configuration has been noted, however, under temporal circumstances which numerous investigators have associated with enhancement of contractility. The significance of this observation requires further study.

References
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