Alternans of Action Potential Duration
After Abrupt Shortening of Cycle Length:
Differences Between Dog Purkinje and Ventricular Muscle Fibers

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The purpose of this study was to determine whether the alternans of action potential duration (APD) occurring in Purkinje and ventricular muscle fibers after an abrupt shortening of cycle length can be explained by the two factors controlling the cycle length–dependent APD changes (i.e., restitution and memory effect). Action potentials were recorded simultaneously from dog Purkinje fibers and ventricular muscle fibers using conventional microelectrode techniques. APD change during alternans was dependent on the preceding diastolic interval in the same manner as during restitution in Purkinje fibers but not in ventricular muscle fibers. The course of memory change was not affected by the presence of alternans in either fiber type. In Purkinje fibers, APD alternans was attenuated by a Ca++ channel blocker, nisoldipine (2 × 10^{-8} M), and augmented by a Ca++ channel agonist, Bay K 8644 (3 × 10^{-8} M). These effects were attributed to the changes in the kinetics and the amplitude of outward current. APD alternans in ventricular muscle fibers was always preceded and accompanied by alternans of action potential shape. Alternans of both action potential shape and APD was suppressed by nisoldipine (2 × 10^{-4} M) and attenuated by Bay K 8644 (3 × 10^{-4} M). These results show that in Purkinje fibers, APD during alternans can be explained by restitution and memory effect. However, in ventricular muscle fibers, the mechanism of APD alternans is linked to factors controlling action potential shape. These findings are compatible with the hypothesis that APD alternans in Purkinje fibers depends on the differences in the recovery of membrane currents generated by the preceding action potential and in ventricular muscle fibers on the differences in the concentration and/or handling of intracellular calcium.

Alternans of action potential duration (APD) is a well-recognized phenomenon that tends to occur at rapid rates of stimulation and after an abrupt shortening of the cycle length. When the rate of stimulation is constant, the short action potential during alternans is followed by a longer diastolic interval (DI) and the long action potential by a shorter DI. It has been suggested that these differences in DI are responsible for the occurrence and maintenance of APD alternans. Hauswirth et al. attributed APD changes during alternans in Purkinje fibers to differences in the magnitude of the decaying time-dependent outward current, but admitted that differences in the reavailability of an inward current could produce similar effects. In either case, APD alternans will not occur in the absence of changing DI.

In the ventricular muscle fibers, APD alternans is associated with alternans in tension and changes in action potential shape. It has been pointed out by Edmans et al. and Greenspan et al. that alternans in the dog ventricular muscle fibers may be limited to changes in action potential shape without changes in APD and preceding DI. Spear and Moore attributed alternans in various types of mammalian ventricular muscle fibers to the influence of some factors associated with contraction. However, it is not clear whether these factors change the shape and duration of action potential, independently of DI.

Boyett and Jewell analyzed in a single experiment alternans of APD occurring simultaneously with tension alternans during rapid stimulation of cat papillary muscle and concluded that both the short and long action potentials during alternans could be explained by changes in the preceding DI. They proposed that the APD alternans induced by stimulation after a long rest resulted from an interaction of the two components responsible for the rate-dependent APD shortening (i.e., electrical restitution and downward displacement of the restitution curve), a process also known as declining memory effect. Yet, this hypothesis does not explain the alternans of action potential shape that occurs without change in APD and DI.

The purpose of the present study was to answer the question of whether the factors controlling the cycle length–dependent APD changes (i.e., the restitution and the declining memory effect) can explain alternans in Purkinje fibers, ventricular muscle fibers, or both. The results of our study suggest that these two
factors can explain alternans in Purkinje fibers but that another mechanism must be postulated to explain alternans in ventricular muscle fibers.

Materials and Methods

Adult mongrel dogs of either sex, weighing 10–15 kg, were anesthetized with sodium secobarbital (30 mg/kg i.v.). Their hearts were removed rapidly through a right thoracotomy and immersed in cool oxygenated Tyrode’s solution. Free running Purkinje false tendons (5–10 mm long, <1 mm diameter) and attached papillary muscle tips (3–10 mm wide, 5–10 mm long, 1–2 mm thick) were excised from either ventricle, affixed to the paraffin floor of a 10 ml Lucite muscle chamber, and superfused with Tyrode’s solution gassed with 95% O2–5% CO2.

The composition of Tyrode’s solution (mM) was Na 148, K 4.0, Cl 127, Ca 2.0, HCO3 22.0, H2PO4 0.9, Mg 0.5, and glucose 5.5, pH after oxygenation 7.3 ± 0.05. The bath temperature was kept constant at 36 ± 0.5°C.

Transmembrane action potentials were recorded simultaneously from Purkinje fibers and ventricular muscle fibers using glass microelectrodes filled with 3 M KCl (DC resistance 10–15 MΩ). Electrical stimuli of 2 msec duration and twice diastolic threshold strength were delivered through Teflon-coated bipolar silver electrodes at ventricular muscle fibers site, about 1–2 mm from the insertion of the false tendon. The preparations were driven at a basic cycle length of 1,000 msec for 2–3 hours before the experiments were begun. The basic cycle length was changed abruptly to a series of short cycle lengths. The shortest cycle length corresponded to the effective refractory period, and the subsequent cycle lengths were increased successively by 20 msec until the cycle length was equal to 2 effective refractory period plus 300 msec. Restitution curves were constructed by plotting the first action potential at each cycle length against the preceding DI. Between each change to a new cycle length for a time sufficient to return to control state. In six preparations, the stimulation at each short cycle length was maintained for 10 minutes, and in the remaining preparations, for 20 seconds.

Action potentials were displayed on an oscilloscope and photographed using a c-5g oscilloscope camera (Tektronix, Beaverton, Oregon). Also, they were stored on magnetic tape and reproduced on a strip chart recorder at a paper speed of 250 mm/sec. We measured APD at 100% repolarization in both fiber types at the intersection of the tangent line fitted to phase 2 by eye with the horizontal line at the level of maximum diastolic potential. DI was measured from this intersection to the upstroke of the following action potential. In the subsequent text, APD refers to APD at 100% repolarization, unless stated otherwise. The duration of action potential was also measured at the level of −60 mV (APD\textsubscript{−60 mV}) and at the level of plateau. The plateau duration (D\textsuperscript{\textcircled{P}}) in Purkinje fibers was measured at the level of the intersection of two tangent lines, one fitted to phase 2 and another fitted to phase 3. In ventricular muscle fibers, D\textsuperscript{\textcircled{P}} was measured at the level of 30% repolarization. APD alternans was defined arbitrarily as the sequence of at least three action potentials where the one in the middle was longer or shorter by ≥4 msec than both the preceding and following action potentials. In a series of experiments, the preparation was superfused with one of two dihydropyridine derivatives (nisoldipine or Bay K 8644). These compounds were kindly supplied by Miles Laboratories, New Haven, Connecticut. Each compound was dissolved in polyethylene glycol 400 to make a concentrated stock solution (10 mM). This solvent had no effect on the slow inward current (i\textsubscript{s}) at concentrations ten times greater than the one used in this study,\textsuperscript{9} and, in our laboratory, had no effect on the shape and duration of action potential at the concentration used in this study (H. Sai toh, J.C. Bailey, and B. Surawicz, unpublished observation). Aliquots of stock solution were diluted in Tyrode’s solution to obtain the working concentrations. The nisoldipine and Bay K 8644 studies were performed in a dark room.

Results are presented as mean ± SEM. In the absence of alternans, the relation between the logarithm of time and decrease of APD was linear in all experiments. Least-squares regression lines were calculated at each cycle length within each experiment. Repeated measures analysis of variance was calculated at each cycle length within each experiment. Repeated measures analysis of variance or paired t tests were used to compare the slopes. In the comparisons of APD change during alternans with APD during restitution, regression lines were compared with the identity line by testing whether the slope differed from 1 and whether the intercept differed from 0. Continuous variables such as APD were analyzed by t test or analysis of variance if three or more groups were present. Since ratios are not normally distributed, these were analyzed using Wilcoxon signed rank test or Friedman’s nonparametric repeated measures analysis of variance. The results were considered significant when p < 0.05.

Results

Purkinje Fibers

Characteristics of action potential. At a basic cycle length of 1,000 msec, the mean values of resting membrane potential, action potential amplitude, and maximum depolarization rate of phase 0 (V\textsubscript{m}) were −88.3 ± 0.4 mV, 120.9 ± 0.6 mV, and 566 ± 23 V/sec, respectively (n = 26). These values were not significantly different from the corresponding values at other cycle lengths used in this study. The APD and D\textsuperscript{\textcircled{P}} at the basic cycle length were 356 ± 10 and 255 ± 6 msec, respectively.

Course of APD change following an abrupt cycle shortening. Figure 1 shows the time courses of changing APD, normalized for the APD at basic cycle length (APD\textsubscript{a}), in a representative experiment in which the cycle length was abruptly shortened to 500, 400, and 300 msec. At each new cycle length, the first APD after the change is shorter than APD\textsubscript{a}, and the second
APD is longer than both the first and third APDs, that is, alternans of APD. At each cycle length, the magnitude of APD alternans, defined as the difference between two consecutive APDs, decreases progressively with time. Similar results were obtained in other experiments.

The duration of APD alternans increased as the cycle length shortened (Figure 1). The average duration of alternans was 1.8 ± 0.2 seconds at cycle length of 500 msec (n = 10), 2.6 ± 0.2 seconds at cycle length of 400 msec (n = 16), and 5.1 ± 1.0 seconds at cycle length of 300 msec (n = 13). In 16 preparations, the longest cycle at which alternans appeared averaged 506 ± 17 msec (range 440–580 msec). The results were not changed when APD in mV was substituted for APD except for a 20-msec decrease of the longest cycle at which alternans appeared in four preparations.

Following the cessation of alternans, APD decreased gradually at each cycle length to a new steady state within about 240 seconds (Figure 1). In six preparations, these times averaged 205 ± 33, 205 ± 25, and 240 ± 24 seconds at cycle lengths of 500, 400, and 300 msec, respectively. The decrease of APD against logarithm of time was linear, and in these six preparations the linear correlation was highly significant at each cycle length (r² ≥ 0.97, p < 0.001). The slopes of decreasing APD averaged −7.3 ± 0.5%, −7.2 ± 0.4%, and −7.1 ± 0.5% APD/log sec at cycle lengths of 500, 400, and 300 msec, respectively, and were not significantly different from each other.

Figure 1 shows that when the lines of decreasing APD at cycle lengths of 400 and 300 msec were extrapolated from the point of the cessation of alternans to the point of its onset (the second action potential), the shorter action potentials during alternans were below and the longer action potentials were above the extrapolated lines. The same results were obtained in five other experiments.

Assuming that the gradual decrease of APD in the absence of alternans reflects the declining memory effect, the deviation of APD from the extrapolated lines of declining memory reveals the presence of an additional factor controlling the APD during alternans. The evidence in support of this deduction is firmer for the shorter than for the longer action potentials because the longer action potentials shorten progressively in a manner consistent with the declining memory effect, while the duration of the consecutive shorter action potentials follows an opposite course.

In the subsequent experiments, we examined whether the deviations of the APD during alternans from the course of declining memory could be attributed to the factors that determine the APD during restitution.

**Figure 2.** Panel A: Relation between action potential duration (APD, ordinate) and preceding diastolic interval (DI, abscissa) during restitution (solid line) and during alternans (scattered symbols) in a Purkinje fiber. ▲, First to fourth action potential after changing cycle length to 380 msec; ■, first to fifth action potential after changing cycle length to 360 msec; ●, first to seventh action potential after changing cycle length to 340 msec; ○, first to eighth action potential after changing cycle length to 320 and 300 msec, respectively. x₁, x₂, duration of second and third action potential at a cycle length of 300 msec; y₁ and y₂, corresponding APDs on restitution curve at common DIs x₁ and x₂. Panel B: Difference between two consecutive APDs during alternans (ΔAPD alternans) is plotted against corresponding difference between two consecutive APDs on restitution curve at common DIs (ΔAPD restitution) for 22 pairs of consecutive action potentials from Figure 2A. Solid line, identity line; interrupted line, fitted to data by linear regression.
Relation between action potential duration and preceding diastolic interval during restitution and alternans. Figure 2A shows a plot of 32 APDs during alternans at five cycles ranging from 300 to 380 msec against the preceding DI in a representative experiment. The solid line shows a portion of restitution curve. It can be seen that the distribution of APDs during alternans (after the second action potential) parallels the course of restitution, but at each common DI, the APD during alternans is shorter than the APD during restitution.

To compare the DI/APD relations during alternans and restitution, we designed a procedure based on previous observations that in Purkinje fibers, APD difference of about 150 msec had no effect on the kinetics of restitution.10 In Figure 2B, we plotted the difference between two consecutive APDs during alternans, designated \( \Delta \text{APD}_{\text{alt}} \), against the difference between two consecutive APDs on the restitution curve, designated \( \Delta \text{APD}_{\text{rest}} \), at common DIs for 22 pairs of consecutive action potentials from Figure 2A. For example, at a cycle length of 300 msec, the difference between the third APD \((x_3)\) and the second APD \((x_2)\) during alternans is -44 msec (220-264 msec), while the difference between corresponding APDs at two points projected on the restitution curve at the same DIs as during alternans \((y_3\) and \(y_2\)) is -42 msec (228-270 msec). The correlation between these two values is highly significant \((r = 0.99, p < 0.001)\), and the slope of the regression line is not significantly different from 1. Similar results were obtained in other experiments at each cycle length.

We also analyzed our results independent of the assumption that APD differences have no effect on the kinetics of restitution. For this, we used a procedure designed by Boyett and Jewell, which is illustrated in Figure 5 in reference 7. Instead of using a single restitution curve, we used a series of restitution curves constructed after each successive action potential during alternans. This procedure puts each APD during alternans on a restitution curve constructed after the preceding action potential.

The inset of Figure 3 shows the application of this procedure in a representative experiment in which the cycle length was changed from 1,000 to 320 msec. The solid line at the top shows a portion of the restitution curve after the third action potential. Below this, from top to bottom, are portions of restitution curves constructed at the basic cycle length, in the presence and in the absence of alternans. The downward deviation from the identity line is not significantly different from 1, but the intercept is shifted by 1.8 msec downward from the identity line.

Declining memory effect in the presence of action potential duration alternans. The finding that the regression line fitted to the relation between \( \Delta \text{APD}_{\text{alt}} \) and \( \Delta \text{APD}_{\text{rest}} \) parallels the identity line but is shifted slightly downward from the identity line means that each APD difference during alternans is slightly but significantly smaller than the corresponding APD difference during restitution. The difference between \( \Delta \text{APD}_{\text{alt}} \) and \( \Delta \text{APD}_{\text{rest}} \) must be attributed to a process that gradually displaces each APD during alternans downward from the restitution curve. We questioned whether this downward deviation can be explained by the declining memory effect. To answer this question, we compared the magnitude of the downward deviation of the APD from the restitution curve constructed at the basic cycle length, in the presence and in the absence of alternans. The downward deviation was expressed as the deviation of the APD from the APD on the restitution curve at a common DI. Figure 4 shows the average values of seven consecutive APD deviations in 16 preparations at three cycle lengths of 500, 400, and 300 msec. At a cycle length of 500 msec, alternans was absent in six preparations, and in the remaining 10, alternans lasted for...
FIGURE 4. Downward deviation of second to eighth APD from restitution curve after changing to three shorter cycle lengths (CL) in 16 Purkinje fibers. Vertical bars shown ±SEM. (For explanation, see text.)

3.6 ± 0.4 cycles. At cycle lengths of 400 and 300 msec, the durations of APD alternans averaged 6.5 ± 0.5 and 17.0 ± 3.3 cycles, respectively. The deviations of the second APD from the restitution curve averaged 5.7 ± 0.6 msec at a cycle length of 500 msec, 9.8 ± 1.5 msec at a cycle length of 400 msec, and 12.9 ± 0.8 msec at a cycle length of 300 msec; these values are significantly different from each other. However, the subsequent deviations from the second to the eighth action potential at these three cycle lengths averaged 8.3 ± 0.9, 8.3 ± 0.7, and 8.5 ± 1.2 msec, respectively. These three values are not significantly different from each other. This suggests that, following the second action potential, the memory declines in the same manner in the absence of alternans as in the presence of alternans of variable duration and magnitude.

Conditions for onset, maintenance, and termination of action potential duration alternans. When APD alternans is induced by an abrupt shortening of cycle, the DI preceding the first action potential is shorter than that preceding the second action potential. During alternans, the sum of the first APD (APD,) and the preceding DI (DIp) is shorter than the cycle length, while the sum of the second APD (APD₂) and the preceding DI (DIp₂) is longer than the cycle length. This sequence continues until alternans terminates (i.e., two consecutive APDs differ from each other by less than 4 msec). Therefore, at the time of termination, the sum of the APD and the preceding DI equals (within 4 msec) the cycle length. We postulated that if the only requirement for the induction and the maintenance of APD alternans is the sequence of (DIp + APD) intervals longer and shorter than cycle length, alternans should be prevented or interrupted at any time by interpolating a single (DIp + APD) interval that is equal (within 4 msec) to the cycle length. We tested this postulate using the procedure shown in Figure 5.

In the top panel in Figure 5, basic cycle length is changed to cycle length of 380 msec. At the onset of alternans, DIp₁ (0 msec) + APD₁ (266 msec) = 266

![Diagram](https://example.com/diagram.png)

FIGURE 5. Prevention and interruption of action potential duration (APD) alternans by interpolation of single cycle in a Purkinje fiber. Top panel: Alternans of initial five action potentials after changing from cycle length (CL) of 1,000 msec (last action potential is shown) to CL of 380 msec. Middle panel: Prevention of alternans when cycle preceding first action potential is increased from 380 to 450 msec. Bottom panel: Interruption of alternans when cycle preceding second action potential is decreased from 380 to 350 msec. Dₚ, plateau duration. (See text.)
msec and $D_{I^2}$ (114 msec) + $APD_1$ (318 msec) = 432 msec. Alternans terminates at the 12th action potential (not shown) when $D_{I^2}$ (84 msec) + $APD_1$ (294 msec) = 378 msec. To test the conditions for prevention of alternans, the first cycle of the train was lengthened by 10-msec increments without altering the subsequent cycle length. Alternans was not prevented by any of the interrupted cycles shorter than 450 msec. The middle strip in Figure 5 shows that the appearance of alternans is prevented when the first cycle is increased to 450 msec; at this time the ($D_{I^2} + APD_1$) interval is 380 msec (i.e., equal to the cycle length).

To test the conditions for interrupting alternans, the second cycle of the train was shortened by 10-msec decrements without altering the subsequent cycle length. Alternans was not prevented by any of the interrupted cycles longer than 350 msec. The bottom panel in Figure 5 shows interruption of alternans when the second cycle is shortened to 350 msec; at this time, the ($D_{I^2} + APD_1$) interval is 382 msec (i.e., 2 msec longer than the cycle length).

The two procedures shown in Figure 5 were repeated at cycle lengths ranging from 320 to 400 msec (average 364 ± 33 msec) in five other preparations. In these six preparations, there was a strong correlation between the ($D_{I^2} + APD_1$) intervals of the cycles introduced to both prevent and interrupt alternans and the cycle length ($r=0.98$, $p<0.001$).

**Ventricular Muscle Fibers**

**Characteristics of action potential.** At the basic cycle length of 1,000 msec, the mean values of resting membrane potential, action potential amplitude, and $V_{max}$ were $-83.0 \pm 0.5$ mV, $110.3 \pm 1.1$ mV, and $195 \pm 7$ V/sec, respectively ($n=26$). These values were not significantly different from the corresponding values at other cycle lengths except for a significant reduction of each value at the cycle length of 250 msec ($-79.5 \pm 1.6$ mV, $102.0 \pm 0.9$ mV, and $170 \pm 14$ V/sec, respectively). The APD and $D_{I^2}$ at basic cycle length were $228 \pm 4$ and $135 \pm 4$ msec, respectively.

**Alternans of action potential duration following abrupt cycle shortening.** Similar to Purkinje fibers, APD alternans in ventricular muscle fibers occurred only at short cycles, and both the magnitude and the duration of alternans increased as the cycle length shortened. However, there were several differences between the characteristics of alternans in the two fiber types. Figure 6 shows that in Purkinje fibers (Panel A), the first action potential is shorter, and in ventricular muscle fibers (Panel B), the first action potential is longer than each of the subsequent action potentials during alternans. In Purkinje fibers, the first action potential was the shortest in all experiments at each cycle length. In ventricular muscle fibers, the first action potential was the longest in 14 of 16 experiments at each cycle length. In the remaining two, the second action potential was longer than the first action.

![Figure 6. Examples of action potential alternans after an abrupt change of cycle length. Panel A: Last action potential at basic cycle length and initial six action potentials after changing to cycle length of 320 msec in a Purkinje fiber. Panel B: Last action potential at basic cycle length and initial eight action potentials after changing cycle length to 240 msec in a ventricular muscle fiber. (Further explanation in text.)](http://circres.ahajournals.org/)

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potential, but this occurred only at the shortest cycle (200 msec in one and 220 msec in the other).

The second major difference between the alternans in Purkinje fibers and ventricular muscle fibers concerns the shape of the action potential. We defined the change in shape arbitrarily as the change in the $D_I/\text{APD}$ ratio. In Figure 6A, the $D_I/\text{APD}$ ratio of the first action potential (56.1%) is smaller than the ratio of the second action potential (65.7%), but after the second action potential, the $D_I/\text{APD}$ ratio decreases gradually without an alternans of this ratio. In Figure 6B, the $D_I/\text{APD}$ ratio of the first action potential (60.4%) is greater than the ratio of the second action potential (44.4%), and the latter is smaller than the ratio of the third action potential (57.8%). This is an alternans of action potential shape that continues (differences between two consecutive $D_I/\text{APD}$ ratios ≥3%) for more than 20 seconds (only first eight action potentials are shown). The action potentials with the greater $D_I/\text{APD}$ ratio have a longer plateau and a steeper course of terminal repolarization and resemble a square, whereas the action potentials with the smaller $D_I/\text{APD}$ ratio have a shorter plateau and a slower course of terminal repolarization and resemble a triangle.

Figure 6B shows that, beginning with the third action potential, alternans of action potential shape is accompanied by an alternans of APD. During alternans, the triangular action potentials are longer than both the preceding and following square action potentials. However, the first action potential, although of square configuration, is longer than the subsequent triangular action potential, which, in turn, is equal in duration to the following square action potential. Thus, the alternans of action potential shape begins immediately after the change to a shorter cycle, whereas the APD alternans begins after the third action potential. Such sequence was present in nine of 10 experiments at 60 of 71 cycle lengths. An alternans of action potential shape without an alternans of APD occurred in one experiment at each of five cycle lengths and in four experiments only at one or two longest cycles. An alternans of APD without an alternans in action potential shape did not occur in any experiment.

The longest cycle at which alternans of action potential shape appeared averaged $384 \pm 18$ msec (range 320–460 msec; $n = 10$), and the longest cycle at which APD alternans occurred averaged $367 \pm 23$ msec (range 280–460 msec; $n = 9$). Substitution of $\text{APD}_{\text{ref}}$ for APD did not change the results qualitatively but in four preparations decreased the values of the longest cycle at which alternans appeared by 20–40 msec.

The average longest cycle at which APD alternans appeared in ventricular muscle fibers was significantly shorter than that in Purkinje fibers ($p < 0.001$). However, the APD at the basic cycle length was $356 \pm 10$ msec in Purkinje and $228 \pm 4$ msec in ventricular muscle fibers. Consequently, the DIs preceding the first action potential at the cycle length at which alternans appeared averaged $171 \pm 7$ msec in Purkinje and $159 \pm 15$ msec in ventricular muscle fibers. These two values were not significantly different from each other. Therefore, the difference between the longest cycles at which alternans appeared in the two fiber types could be explained by the APD difference at the basic cycle length.

**Diastolic interval/action potential duration relations during restitution and alternans.** Figure 6B shows that the first action potential, preceded by a DI of 16 msec, is longer than the second action potential, preceded by a DI of 48 msec (i.e., a relation opposite to the DI/APD relation during restitution). At the same time, the second and third action potentials are of equal duration although they are preceded by different DIs. This shows that the DI/APD relation during alternans does not resemble the DI/APD relation during restitution.

Figure 7A shows a plot of 40 APDs during alternans at five cycles ranging from 220 to 300 msec against the preceding DI in a representative experiment. The solid line shows a portion of the restitution curve. The figure shows that, unlike in Purkinje fibers (Figure 2A), the distribution of APDs during alternans (after the second action potential) does not parallel the course of restitution. This is also seen in Figure 7B where $\Delta \text{APD}_{\text{ref}}$ was plotted against the corresponding $\Delta \text{APD}_{\text{ref}}$ for 30 pairs of consecutive action potentials from Figure 7A. The same results were obtained in eight other experiments at each cycle length.

In four other experiments (three at a cycle length of 240 msec and one at 260 msec), the procedure shown in Figure 3 for Purkinje fibers was used to compare the DI/APD relation during alternans and restitution. Unlike in Purkinje fibers, the slope of regression line fitted to the data ($2.03$) differed significantly from 1 ($p < 0.05$).

**Figure 7.** Panel A: Relation between action potential duration (APD, ordinate) and preceding diastolic interval (DI, abscissa) during restitution (solid line) and during alternans (scattered symbols) in a ventricular muscle fiber. ○, △, ◇, ▽, First to eighth action potentials after changing cycle length to 200, 280, 260, 240, and 220 msec, respectively. Panel B: $\Delta \text{APD}_{\text{ref}}$ is plotted against $\Delta \text{APD}_{\text{ref}}$, as defined in the legend to figure 2 for 30 pairs of consecutive action potentials (from second to eighth) from Panel A. Solid line, identity line.
We concluded that APD change during alternans cannot be explained by the mechanism that controls the DI/APD relation during restitution. This conclusion was also supported by the results of experiments in which alternans was prevented (n = 6) or interrupted (n = 4) by interpolating a single cycle. Unlike Purkinje fibers, the (DI + APD) intervals required to prevent or terminate alternans correlated poorly with the cycle length (r = 0.08; p = NS).

**Course of action potential duration change following abrupt cycle shortening.** Figure 8 shows the behavior of APD, normalized for the APD, in a representative experiment in which the cycle was abruptly shortened to 500, 400, 300, and 250 msec. Both in the absence (cycle length, 500 and 400 msec) and presence of alternans (cycle length, 300 msec), the slope of APD decline to a new steady state against the logarithm of time is biphasic with a slower course about 6 seconds, the durations of both the longer and shorter action potentials declined linearly against logarithm of time. These times are not significantly different from the late slopes at cycle length of 300 msec (−8.2 ± 2.7% APD/log sec) in the same experiments. This suggests that the memory declines in the same manner in the presence of APD alternans as in its absence.

**Effect of Nisoldipine**

Two groups of investigators showed that APD alternans can be suppressed or attenuated by the slow channel-blocking drugs verapamil or diltiazem. To compare the effect of a slow channel-blocking drug on alternans in Purkinje fibers and ventricular muscle fibers, nisoldipine was used, a compound reported to be a potent and selective blocker of the calcium current.

**Purkinje fibers.** In five preparations, 2 x 10⁻⁶ M nisoldipine concentration produced no significant changes in resting membrane potential, action potential amplitude, or Vmax. At basic cycle length of 1,000 msec, nisoldipine shortened APD from 343 ± 14 to 327 ± 18 msec, shortened Dp from 223 ± 6 to 194 ± 9 msec.
msec, and decreased Dp/APD ratio from 65.3 ± 1.3% to 57.4 ± 2.6%. Each of these changes was significant.

To obtain in the presence of nisoldipine an APD, that is nearly equal (within 4 msec) to that in control, we increased the basic cycle length in the presence of nisoldipine to an average value of 1,240 ± 89 msec (range, 1,100–1,300 msec). In the absence of nisoldipine, such increase in basic cycle length did not attenuate APD alternans (H. Saitoh, J.C. Bailey, and B. Surawicz, unpublished observations).

Nisoldipine shortened significantly the longest cycle at which alternans appeared from 512 ± 17 to 472 ± 17 msec. Nisoldipine also decreased the magnitude of alternans. For example, at the shortest cycle of 320 ± 14 msec (range 300–360 msec), the difference between the first and second APDs decreased from 76 ± 9 to 58 ± 6 msec (p < 0.01) and that between the second and third APDs decreased from 36 ± 4 to 25 ± 3 msec (p < 0.01). Also, the differences between the subsequent consecutive APDs were significantly smaller than the corresponding control differences. Similar changes occurred at longer cycles. Nisoldipine did not abolish alternans in any of these experiments or in two additional experiments in which the concentration was increased to 10⁻⁵ M; the latter concentration was reported to block i^ completely.¹¹

The observed attenuation of alternans by nisoldipine (i.e., a lesser change in APD at any given DI change) could be due to either slower kinetics of restitution or altered DI/APD relation during alternans with respect to restitution. We examined both variables.

The restitution curve was described by the following equation:

\[
\text{APD}_t = \text{APD}_0 [1 - A \exp (-t/T)]
\]

where APD represents the APD preceded by DI of t, A the amplitude, and T the time constant of exponential component. Within the range of DIs shorter than 200 msec, the correlation coefficient between APD, and exponential component of the fitted equation was ≥0.98 with and without nisoldipine. Nisoldipine prolonged significantly the time constant (T) of this restitution component from 152 ± 7 to 170 ± 9 msec (p < 0.01) and decreased significantly the amplitude (A) from 0.36 ± 0.01 to 0.32 ± 0.01 (p < 0.05).

We compared the DI/APD relation during restitution and during alternans in a previously described manner. Figure 9 shows the plot of ΔAPD_ac against the corresponding ΔAPD_ac at cycle lengths averaging 320 ± 14 msec (range 300–360 msec). These were the shortest cycles in each of the five experiments. The correlation between these two values is highly significant (r = 0.99, p < 0.001), and the slope of the regression line is not significantly different from 1. This shows that nisoldipine did not alter the DI/APD relation during alternans from that during restitution and suggests that nisoldipine attenuated alternans as a result of slower kinetics and decreased amplitude of restitution.

**Ventricular muscle fibers.** In five preparations, 2 × 10⁻⁴ M nisoldipine produced no significant changes in resting membrane potential, action potential amplitude, or V_m. At basic cycle length of 1,000 msec, nisoldipine shortened APD from 214 ± 7 to 198 ± 12 msec, shortened Dp from 117 ± 6 to 98 ± 6 msec, and decreased Dp/APD ratio from 54.9 ± 1.2% to 49.5 ± 0.8%. Each of these changes was significant.

Before nisoldipine, alternans of action potential shape appeared in each experiment at four to eight cycle lengths, and each alternans of action potential shape was followed by an alternans of APD after the third action potential. Nisoldipine prevented the occurrence of alternans of both action potential shape and duration at each cycle length in four of five preparations. In one preparation, nisoldipine did not prevent alternans but reduced by 62 ± 10% the magnitude of action potential shape alternans and by 52 ± 5% the magnitude of APD alternans, measured between the seventh and eighth action potentials, at seven cycle lengths ranging from 220 to 340 msec.

Figure 10A shows superposition of action potentials at the onset of alternans when the cycle length was changed from 1,000 to 240 msec in the absence (continuous line) and presence (interrupted line) of nisoldipine. It can be seen that nisoldipine lowered the plateau of both the square and triangular action potentials but had a greater effect on the shape of the square than of the triangular action potential. At a cycle length of 240 msec, in this and four other experiments, nisoldipine reduced significantly the Dp/APD ratio of the following square action potentials: first action potential, from 62.5 ± 1.8% to 50.9 ± 1.9%; third action potential, from 57.8 ± 1.0% to 45.5 ± 1.3%; fifth action potential, from 57.3 ± 1.2% to 43.0 ± 1.6%; and seventh action potential, from 57.4 ± 1.2% to 42.8 ± 1.9%. In contrast, the drug induced no significant change in the Dp/APD ratio of the following triangular action potentials: the second, the fourth, the sixth, and the eighth. Similar results were obtained at other cycle lengths.

We concluded that the alternans of APD failed to appear when nisoldipine suppressed the alternans of action potential shape and that this effect occurred because nisoldipine depressed the plateau of the square action potential more than that of the triangular action potential.

**Effect of Bay K 8644**

The effect of nisoldipine on alternans in ventricular muscle fibers suggests that the APD alternans is related to the mechanism controlling the plateau of the action potential. To further test this relation, we used Bay K 8644, a compound that shifts the plateau to a more positive membrane potential, presumably due to enhanced inward current flowing through the calcium channel.¹³

**Purkinje fibers.** In five preparations, 3 × 10⁻⁸ M Bay K 8644 concentration produced no significant changes in the resting membrane potential, action potential amplitude, or V_m. At basic cycle length of 1,000 msec, Bay K 8644 lengthened APD from...
331 ± 18 to 340 ± 18 msec ($p<0.05$), lengthened $D_d$ from 231 ± 19 to 243 ± 20 msec ($p<0.05$), and increased $D_d/APD$ ratio from 69 ± 2% to 71 ± 3% (NS). To obtain in the presence of Bay K 8644 an APD, that is nearly equal (within 4 msec) to that in control, we decreased the basic cycle length in the presence of Bay K 8644 to an average value of 930 ± 23 msec (range 900–980 msec). Bay K 8644 did not abolish alternans in any experiment and did not change the longest cycle at which alternans appeared but increased slightly the magnitude of alternans. For example, at the shortest cycle length of 320 ± 14 msec (range 300–360 msec), the difference between the first and second APDs increased from 86 ± 13 to 91 ± 12 msec ($p<0.05$) and that between the second and third APDs from 45 ± 8 to 49 ± 8 msec ($p<0.05$). Also, the differences between the subsequent consecutive APDs were significantly greater than the corresponding control differences. Similar changes occurred at longer cycles.

The restitution curve was described by the equation shown in the previous section. Within the range of DIs shorter than 200 msec, the correlation coefficient between APD, and exponential component of the fitted equation was ≥0.97 with and without Bay K 8644. Bay K 8644 shortened slightly but significantly the time constant of this restitution component from 148 ± 9 to 142 ± 8 msec without changing the amplitude of restitution (0.39 ± 0.02 to 0.38 ± 0.02, $p=NS$).

We also compared the DI/APD relation during restitution and alternans in a previously described manner. At the shortest cycles averaging 320 ± 14 msec (range 300–360 msec), the correlation between $\Delta APD_{n}$ and the corresponding $\Delta APD_{m}$ is highly significant ($r=0.99$, $p<0.001$), and the slope of the regression line is not significantly different from 1. This suggests that the slight augmentation of alternans by Bay K 8644 resulted from its effect on the kinetics of restitution.

**Ventricular muscle fibers.** In 14 preparations, $3 \times 10^{-8} M$ Bay K 8644 produced no significant changes in resting membrane potential, action potential amplitude, or $V_n$. At basic cycle length of 1,000 msec, Bay K 8644 lengthened APD from 218 ± 4 to 235 ± 4 msec, lengthened $D_d$ from 121 ± 3 to 143 ± 3 msec, and increased $D_d/APD$ ratio from 56 ± 2% to 61 ± 1%. Each of these changes was significant. The restitution curves normalized for APD, with and without Bay K 8644, were superimposable in each preparation.

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**Figure 10.** Superposition of action potentials in absence of (continuous line) and presence of (interrupted line) nisoldipine (Panel A) and Bay K 8644 (Panels B and C) in ventricular muscle fibers. Panel A: Effect of nisoldipine ($2 \times 10^{-8} M$) on last action potential at basic cycle length and on first to seventh action potentials after a change to cycle length of 240 msec. Panel B: Effect of Bay K 8644 ($3 \times 10^{-8} M$) on the seventh and eighth action potentials after change to cycle length of 240 msec. Panel C: Effect of Bay K 8644 ($3 \times 10^{-7} M$) on seventh and eighth action potentials after change to cycle length of 240 msec in same preparation as for Figure 11B. (Further explanation in text.)
We approached the analysis of alternans by correlating the APD changes during alternans with the course of restitution and with the effect of declining memory in Purkinje fibers and ventricular muscle fibers.

Alternans and Kinetics of Restitution

APD during alternans was determined by the preceding DI in the same manner as during restitution in Purkinje fibers but not in ventricular muscle fibers. Also in Purkinje fibers but not in ventricular muscle fibers, alternans could be prevented or interrupted by interpolating a single cycle in which the sum of APD and its preceding DI was equal to the cycle length of stimulation. Furthermore, consistent with the dominant role of restitution in controlling APD during alternans in Purkinje fibers was the attenuation of alternans by nisoldipine that prolonged the time constant of restitution and the augmentation of alternans by Bay K 8644 that accelerated restitution.

The reported effects of slow channel blockers on the kinetics of restitution have varied. Thus, verapamil slowed the fast component of restitution,4,13 but cobalt had no significant effect on this process.19 In this study, nisoldipine prolonged the time constant of the monoexponential early portion of restitution. A similar lengthening of the fast component of restitution in dog Purkinje fibers was found in other experiments in which a longer course of restitution fitted a sum of a fast and a slow exponential component (A. Varro, Y. Nakaya, V. Elharrar, and B. Surawicz, unpublished observations). The effect of Bay K 8644 on restitution has not been studied previously.

Action Potential Duration Decline to New Steady State

Previous studies have shown that the time course of the gradual decrease of APD or the action potential area after cycle length shortening was either monoeponential (Gibbs et al16 in rabbit ventricular muscle fibers, Miller et al17 in dog ventricular muscle fibers and Purkinje fibers, Boyett and Fedida18 in dog Purkinje fibers) or linear when plotted against logarithm of cycle (Vick2 in dog Purkinje fibers). However, no quantitative comparisons between the two fiber types have been reported. In our present study, adjustment to the new steady-state duration was slower in ventricular muscle fibers than in Purkinje fibers at each cycle length. This difference was most pronounced during the early period of about 6 seconds when the slope in ventricular muscle fibers was nearly flat.

Another difference between the APD adjustment to the new steady state in Purkinje and ventricular muscle fibers was related to the different effects of the cycle length. In the Purkinje fibers, the slopes of APD adjustment to the new steady state were not significantly different from each other within the 300–500 msec range of cycle lengths. This suggests a purely time-dependent process of memory dissipation. In ventricular muscle fibers, the slope was significantly steeper at the cycle length of 300 msec than at the two

Discussion

After an abrupt change to a shorter cycle, APD adjusts gradually to a new steady-state value. During this adjustment, APD is subjected to two opposing influences (i.e., restitution and declining memory).7,50 During restitution, APD lengthens with increasing preceding DI, whereas the effect of declining memory results in shortening of each consecutive APD and lengthening of each consecutive DI. In the absence of alternans, the influence of restitution is not detectable during the adjustment of APD to the new steady-state value.

In control, alternans of action potential shape appeared in each experiment, and each alternans of action potential shape was followed after the third action potential by an alternans of APD. Bay K 8644 did not suppress but attenuated alternans of action potential shape in each experiment. This occurred because Bay K 8644 had a more pronounced effect on the plateau of the triangular action potential than on that of the square action potential. Figure 10B shows the effect of Bay K 8644 on the seventh and eighth action potentials during alternans in a representative experiment in which the cycle length was changed to 240 msec. Bay K 8644 increased the Dp of the seventh action potential by 12 msec and that of the eighth action potential by 28 msec. This effect decreased both the difference of action potential shape and the magnitude of APD alternans between these two action potentials. In this and in 13 other experiments, the magnitude of both action potential shape and APD between the seventh and eighth action potentials decreased significantly from 14.8 ± 1.8% to 9.1 ± 1.5% and from 7.9 ± 1.5 to 4.7 ± 1.7 msec, respectively, at the shortest cycle length (average 249 ± 5 msec, range 220–280 msec). Similar results were obtained at other cycle lengths.

In five out of 14 preparations, 3 × 10^{-4} M Bay K 8644 concentration was maintained for 60 minutes and then increased to 3 × 10^{-3} M. This increase produced no significant changes in resting membrane potential, action potential amplitude, \( V_{max} \) or Dp/ADP ratio but caused a significant lengthening of APD and Dp at basic cycle length to 244 ± 8 and 154 ± 8 msec, respectively. Figure 10C shows that although the effect on the plateau of square action potential at this concentration is greater than that of the lower concentration in figure 10B, the corresponding effect on the plateau of triangular action potential is smaller. Such a difference was found in three of five experiments. In each of these three experiments, the alternans of action potential shape was more pronounced at the higher than at the lower Bay K 8644 concentration. At the same time, the relation between the shape and the duration of action potential during alternans was reversed (i.e., the square action potential became longer than the triangular one). In the remaining two experiments, higher Bay K 8644 concentrations caused no significant additional effect on the alternans of either action potential shape or APD.

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longer cycles. This suggests that in these fibers the process of memory dissipation is influenced by some other factor or factors such as the number of action potentials or the duration of diastolic intervals.

Figure 11 shows the relation between the slope of APD adjustment to the new steady state and the sum of diastolic intervals during the time interval from 6 to 180 seconds after the change to a new cycle length. This period contained 580 action potentials at the cycle length of 300 msec, 435 action potentials at 400 msec, and 348 action potentials at 500 msec. There are no significant differences between the slopes at the three cycles in Purkinje fibers, but in ventricular muscle fibers, the slope becomes progressively less negative, that is, less steep with increasing sum of diastolic intervals (r = 0.51, p < 0.05) and decreasing number of action potentials (r = 0.55, p < 0.05). This behavior suggests that either the process accelerating the dissipation of memory in ventricular muscle fibers resides in the action potential or that the process retarding the memory dissipation resides in the diastolic interval. We cannot distinguish between these two possibilities.

In Purkinje fibers, the deviation of the second action potential from the course of restitution increased at shorter cycles. We could not determine whether this cycle length-dependent effect was caused by differences in the declining memory or by an influence of other unidentified factors. However, the subsequent deviation from the course of restitution was not altered by the presence of alternans. Also in both fiber types, the presence of alternans of variable duration did not alter the course of APD decline to the new steady state. We concluded that the role of declining memory in controlling APD was the same in the presence as in the absence of alternans.

Relation Between Shape and Duration of Action Potential in Ventricular Muscle Fibers

In agreement with earlier observations, there was no consistent relation between the duration and the shape of action potential in ventricular muscle fibers. The first action potential of square configuration was longer than the following triangular action potential, but subsequently the triangular action potentials were usually longer than the square action potentials when measured at both the end and the -60-mV level of repolarization.

Our study shows that in ventricular muscle fibers, APD alternans did not occur in the absence of alternans of action potential shape. When the latter was abolished by nisoldipine, APD alternans disappeared. This was associated with shortening of plateau and an increased triangularization of action potential shape. Conversely, attenuation of action potential shape alternans by $3 \times 10^{-4}$ M Bay K 8644 was associated with lengthening of plateau and a more square action potential configuration. These two findings suggest that the alternans of action potential shape and the associated APD alternans result from the differences in plateau currents generated by the preceding action potential. In this study, the former mechanism appeared to operate in ventricular muscle fibers, and the latter in Purkinje fibers. However, both had in common the requirement of a critically short DI for the occurrence and maintenance of alternans.

The hypothesis that the shape of ventricular action potential during alternans was determined primarily by the current modulating the repolarization of their own action potential does not exclude the additional influence of currents generated by the preceding action potential. In particular, the square action potential may be expected to generate a stronger and/or longer-lasting outward current that could accelerate the repolarization of the following action potential. However, this would make it difficult to explain why the triangular action potential was longer than the square one. Also, the shortening effect of the repolarizing current generated by the preceding action potential should be more pronounced in closer proximity to the repolarization (i.e., at a shorter DI). However, this was not the case.

What Controls Action Potential Shape in Ventricular Muscle Fibers?

A longer plateau duration and a plateau shift to a more positive potential of the square shape action potential is most likely due to a greater net contribution of the depolarizing (presumably slow inward) current to the process of repolarization. The triangular
shape of the action potential may reflect a lesser net contribution of depolarizing current to the repolarization process. The weaker tension accompanying the square versus the triangular action potential (references 2–4 and H. Saitoh, J.C. Bailey, and B. Surawicz, unpublished observations) suggests that the square action potential is associated with a smaller amount of free intracellular Ca2+. The decreased intracellular free Ca2+ may contribute to the positive shift and lengthening of the plateau by increasing the driving force for Ca2+, by slowing the inactivation of the Ca2+ current, or by decreasing the conductance of one or more outward currents. The more rapid course of terminal repolarization of the square action potential may be attributed to an increased K+ conductance as a consequence of longer plateau duration and a plateau shift to a more positive potential level. Our present study provides no insight into the mechanisms controlling the above repolarization processes, except to show that the alternans dependent on the critical short cycle length can be suppressed by agents causing both an increase and a decrease of Ca2+ inflow through the slow channel. These findings are consistent with the assumption that this type of alternans results from an imbalance between the amount of available intracellular Ca2+ and the time needed to use it. Similar hypotheses have been postulated by others. Their validity is supported by the recent observations that the intracellular calcium content oscillates at the beginning of repetitive stimuli following a long rest period.

Effect of Bay K 8644 on Action Potential in Ventricular Muscle Fibers

Bay K 8644 prolongs the mean open time of calcium channels and increases calcium influx during the action potential. This results in an increased plateau duration and a shift of the plateau to a more positive potential. The 3 x 10^{-8} M Bay K 8644 concentration had a more pronounced effect on the plateau of the triangular than on that of the square action potential; this resulted in attenuation of APD alternans. The effect on the plateau of the square action potential was further increased by the higher Bay K 8644 concentration (3 x 10^{-7} M). However, the higher concentration caused no further attenuation of alternans because the plateau level of the triangular action potential was elevated less by the higher than by the lower Bay K 8644 concentration.

There are several possible explanations of the paradoxical lessening effect of higher Bay K 8644 concentration on the plateau of the triangular action potential. Thus, it has been shown that at certain concentrations and at certain membrane potentials, the antagonistic effect of Bay K 8644 may outweigh its agonist effect on the currents flowing through the Ca2+ channel. This was unlikely in our experiments because the tension was not depressed but further augmented at the higher Bay K 8644 concentration (H. Saitoh, J.C. Bailey, and B. Surawicz, unpublished observations). A greater influx of calcium caused by higher Bay K 8644 concentration may antagonize the effect of Bay K 8644 on repolarization by faster inactivation of the Ca2+ current, an increased conductance of outward current(s), or both. In addition, Bay K 8644 may accelerate the inactivation of Ca2+ current by a direct action. These effects may be more pronounced in the presence of higher free intracellular calcium associated with a triangular action potential shape. Figures 10B and 10C show that the higher concentration of Bay K 8644 did not augment the effect of lower Bay K 8644 concentration on the terminal repolarization of triangular action potential (i.e., the higher concentration had no effect expected from an increased K+ conductance). Thus, the most likely explanation of the lessening effect on the plateau of the triangular action potential by a higher Bay K 8644 concentration is a more rapid inactivation of the inward current flowing through the calcium channel.

Limitation of Study

Our conclusions concerning the basic differences underlying the mechanism of alternans in Purkinje fibers and ventricular muscle fibers apply only to the studied preparation and the method used to elicit the APD alternans. Boyett and Jewell showed an example of an APD alternans induced by stimulation after a long rest in cat papillary muscle at 30°C. In this, the first action potential is shorter than the second action potential, the longer action potential is preceded by a longer DI, and there is no alternans of action potential shape (Figure 5 in reference 7). This suggests that in some species, under certain conditions, an alternans of APD in ventricular muscle fibers may depend entirely, or in part, on a mechanism similar to that operating in Purkinje fibers. However, in this study, no evidence of such a mechanism was found, even in those two cases of alternans in ventricular muscle fibers where the first action potential was shorter than the second one.

Relation to Findings In Vivo

Alternans of APD in ventricular muscle fibers is believed to result in the alternans of T wave and in the alternans of effective and functional refractory periods. In the study by Janse et al, alternans of effective refractory period in open-chest dogs began with the third beat following the change to a shorter cycle. In our present study, alternans of APD appeared also after the third action potential, even though the alternans of action potential shape was present at the onset. Most likely, the alternans of action potential shape cannot be detected by measuring the effective and functional refractory periods.

In man, Tchou et al observed after a sudden increase in the rate of ventricular pacing an alternans of refractory period in the His-Purkinje system but no concomitant alternans of refractory period in the right ventricular myocardium. Our findings can explain these results because the induction of alternans in ventricular muscle fibers may require a shorter critical cycle length than in Purkinje fibers.
Conclusion

Alternans of APD, induced by an abrupt change to a shorter cycle, is associated with an incomplete recovery of some of the factors controlling the APD. The results of our present study are consistent with the explanation that the alternans of APD in Purkinje fibers depends on the recovery kinetics of the membrane currents generated by the preceding action potential and with the hypothesis of Boyett and Jewell that APD during alternans is controlled by the combined effects of restitution and declining memory. However, this hypothesis does not explain our findings in ventricular muscle fibers, where the differences in APD are linked to the differences in action potential configuration, presumably reflecting differences in handling of the intracellular calcium.

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Key Words • action potential duration • electrical restitution • alternans of action potential • slow inward current
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