Durations of Transmembrane Action Potentials and Functional Refractory Periods of Canine False Tendon and Ventricular Myocardium: COMPARISONS IN SINGLE FIBERS

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The relationship between the functional refractory periods of the specialized cardiac conduction system and of the ventricular muscle is of major importance in the genesis of ventricular fibrillation by a single premature beat arising in the specialized conducting system. Wiggers and Wegria\(^1\) demonstrated that premature ventricular excitation must occur in late systole during the inscription of the T wave in order for ventricular fibrillation to be initiated by a single premature stimulus, i.e., excitation must occur in the functional refractory period of ventricular fibers. If the functional refractory period of Purkinje tissue exceeds that of the ventricular muscle, an early premature discharge in the Purkinje system or an impulse transmitted from the A-V node could not excite the ventricles sufficiently early to cause ventricular fibrillation; excitation of ventricular muscle via the Purkinje system would by necessity occur after expiration of the ventricular vulnerable period. However, if the Purkinje tissue has a functional refractory period equal to or less than that of ventricular muscle, a premature systole conducted over the Purkinje system might invade the ventricles during the "vulnerable" period and lead to ventricular fibrillation.

In vitro studies on action potential durations and functional refractory periods of Purkinje and ventricular muscle fibers have consistently indicated that the Purkinje fibers have a longer functional refractory period.\(^2\) In vivo studies, however, have not been in agreement. Some investigators find no essential difference between in vitro and in vivo results, i.e., the functional refractory period of Purkinje tissue exceeds that of ventricular muscle in vivo.\(^2\) Other in vivo data suggest that the Purkinje tissue may have a shorter refractory period than ventricular muscle.\(^3-5\) If the latter relationship were true, ventricular fibrillation could be caused by a single premature beat arising in the A-V transmission system.

Our preliminary in vitro studies agreed with previously reported in vitro results, i.e., single Purkinje units consistently had longer functional refractory periods than myocardial units in the same preparation under the standard experimental conditions described under Methods. The primary purpose of this study was to determine what variables, if any, would alter differentially the functional refractory periods of Purkinje and ventricular muscle fibers. If conditions could be found where the Purkinje tissue has a briefer functional refractory period than ventricular muscle, then, under these conditions, premature excitation of the Purkinje system could lead to ventricular fibrillation.

Methods

Dogs of differing ages weighing 10 to 20 kg were anesthetized intravenously with pentobarbi-
tional sodium (30 mg/kg) and maintained on artificial respiration. The sternum was split along its midline and the chest walls retracted; then the heart was removed and placed immediately in continuously oxygenated Tyrode's solution. The false tendon network running between the anterior papillary muscle and free wall of the right ventricle and the left anterior and posterior networks of false tendons with attached left ventricular muscle were rapidly removed and stored in a separate oxygenated bath (23°C) until studied in the muscle chamber. Tissue from the right ventricular free wall was removed for comparative studies of the "epicardium" and "endocardium." The heart was continuously immersed in oxygenated Tyrode's solution during the dissection.

SOLUTIONS AND DRUGS

The composition of the Tyrode's solution in millimoles/liter was: NaCl 136.87; KCl 2.68; NaH₂PO₄ 0.41; CaCl₂ 1.80; MgCl₂ 1.12; dextrose 5.5; NaHCO₃ 11.90 and distilled, de-ionized water to make 1,000 ml. When plasma was used to perfuse the isolated tissue, arterial blood was obtained from a femoral artery cannula in dogs anesthetized with pentobarbital. The collected blood was heparinized and centrifuged. During perfusions the plasma was oxygenated with 95% oxygen and 5% carbon dioxide.

The following drugs were used: Z-epinephrine tartrate; acetylcholine iodide; and tris buffer (2-amino-2-hydroxy-methyl 1, 3 propanediol). The tris buffer was added at varying concentrations to the reservoir of Tyrode's solution; fresh solutions of the other drugs were added directly to the muscle chamber in volumes not exceeding 1 ml.

PERFUSION CHAMBER

The muscle chamber was made of lucite lined with paraffin and had a final volume of 40 ml (fig. 1). Oxygenated Tyrode's solution was perfused continuously through the chamber at the rate of about 120 drops per minute by a gravity flow arrangement. The rate was observed by means of a drop counter and could be increased to facilitate flushing the chamber, or decreased to maintain a constant concentration of a drug administered directly into the perfusion chamber. Solutions in the perfusion chamber were maintained at 37°C (±1°C). The level of the solution in the chamber was kept constant by an overflow tube, and an outlet tube at the bottom permitted rapid drainage. The tissue preparation was held lightly by small pins.

RECORDING SYSTEM

Microelectrodes of pyrex capillary glass were pulled to a tip diameter of less than 1 μ and filled with 3 molar KCl under reduced pressure. Suitable electrodes had a final resistance of 10 to 30 megohms. Single cardiac cells were impaled under direct visualization using a Brinkman micromanipulator with an independent vertical control. Electrodes were attached to a silver-silver chloride wire in a manner similar to the method described by Woodbury and Brady. A silver-silver chloride indifferent electrode was immersed in the Tyrode's solution bathing the tissue preparation.

The silver wire attached to the micropipette...
was led into a Grass P-7 high impedance cathode follower. The output of the cathode follower was led single-ended into a dual beam Tektronix 502 cathode ray oscilloscope (CRO) (fig. 1). When simultaneous recordings were taken from the false tendons and papillary muscle, two Grass P-7 cathode followers were used and the signals were displayed on the dual beam CRO. Intracellular action potentials displayed on the CRO were studied directly, or recorded on film with a Grass kymograph camera. A Tektronix 162 waveform generator and a 161 pulse generator were used to generate pulses for time standards.

**STIMULATING SYSTEM**

Driving stimuli were delivered to the false tendon or papillary muscle by means of bipolar electrodes made of Nichrome (diameter about 0.020 inch) or silver-silver chloride wire (0.020 inch in diameter). A two-way switch permitted rapid selection of either the false tendon or papillary muscle stimulating electrodes. These same electrodes were also used to elicit extra-systoles.

The stimulation circuits used in these experiments were similar to those described previously by Mendez et al.7 Stimuli were passed from two Grass S-4 stimulators, wired in series, and modified so that a train of three stimuli with independently variable parameters could be delivered through the same electrodes (fig. 1). The basic drive stimulator (S1) was used to stimulate the preparation at a predetermined rate. A counter interposed between the S1 and S2 stimulators permitted a test pulse to be delivered with variable delay after each sixth or eighth S1 pulse. The S2 pulse was used to estimate the duration of the functional refractory period (FRP) of the basic cycle.

The second stimulator was modified to permit an S3 pulse to be triggered at variable intervals following the S2 stimulus. This permitted the FRP of the premature response initiated by S2 to be determined.

To provide time for possible spontaneous or repetitive responses to the test stimuli, an output from the counter was used to trigger a pulse blocking relay, which for a given period would interrupt the output of the basic drive stimulator (S1). This relay did not interfere with the rhythm of the driving oscillator or the counter.

All stimuli were biphasic pulses of 3.5 msec duration. S1 was set at a voltage which was twice threshold. S2 and S3 were set at values three to five times threshold.

**DEFINITION OF FUNCTIONAL REFRACTORY PERIOD**

The functional refractory period (FRP) is defined as the shortest possible interval between two propagated responses. The true FRP can be obtained only when the stimulus-response distance is negligible. In these studies the stimulus-response distance varied from 1 to 8 mm; the FRP error is equal to the difference in conduction time between the first response and that of the earliest premature response. Therefore, the FRP as recorded is somewhat longer than the true FRP. The action potential durations (APD) were measured as the interval between depolarization and full repolarization. When alternation of action potential duration occurred at rates of 4/sec and above, the durations (determined as the interval between depolarization and maximum repolarization) of two successive action potentials were averaged.

**Results**

There are a number of variables that might change differentially the functional refractory periods (FRP) and action potential durations (APD) of Purkinje and ventricular muscle fibers. The influence upon the FRP and APD of Purkinje and myocardial fibers of changes in the perfusion conditions, the addition of various drugs, and changes in preceding cycle length are presented below. Action potential durations and functional refractory periods were both recorded since these two measurements tend to parallel one another.

**A. EFFECTS OF CHANGES IN PERFUSION CONDITIONS**

One important factor in studies on isolated tissue is the immediate effect, if any, of isolation of the tissue. To determine whether differences in the action potential duration (APD) and functional refractory period (FRP) of false tendon and ventricular muscle fibers were time dependent, transmembrane action potentials were recorded in several preparations within three to four minutes after removal of the tissue from the animal. The action potential duration and functional refractory period of the false tendon cells and papillary muscle fibers were determined at cycle lengths between 333 msec and 1,000 msec, at various times up to four or five hours after isolation of the preparation. No consistent time-related changes were found. The values recorded for false tendon always exceeded those for muscle fibers.

False tendon action potential durations and functional refractory periods still exceeded those of papillary muscle at basic cycle
lengths between 300 and 1,000 msec when:
(a) blood or plasma was substituted for
Tyrode's solution, (b) various concentrations
of tris buffer were added to the perfusion
solution, and (c) when the temperature was
altered between 28 and 41°C.

Since autonomic mediators normally in-
fluence cardiac cells in vivo, the low con-
centrations of these substances in vitro might
cause differential effects upon action po-
tential durations of false tendon and ven-
tricular muscle fibers. However, false ten-
don action potential durations still exceeded
those of papillary muscle following addition
of epinephrine \((0.61 \times 10^{-6} \text{M})\) to \(12.2 \times 10^{-6} \text{M}\)
or acetylcholine \((0.1 \times 10^{-3} \text{M})\) to \(5 \times 10^{-3} \text{M}\),
or the addition of these autonomic
mediators together. Automatic activity, rang-
ing from coupled rhythms to rapid tachycar-
dias, was observed after adding epinephrine
to the perfusion fluid. The pacemaker in all
cases was located in the false tendons and
never in ventricular muscle cells. Premature
false tendon responses, following epinephrine
administration, were identical in form to those
provoked by premature electrical stimulation
and were followed by activity in the ventricu-
lar muscle units.

Although the effects of changes in the ex-
tracellular concentrations of potassium, cal-
cium, and sodium have been studied in both
canine ventricular muscle and Purkinje fibers,2
simultaneous recordings to determine whether
differential effects of changes in the ionic me-
dia occur in these two cardiac tissues, have
not been reported. We found that lowering
K\(^+\) from 2.7 mM/liter to 0.67 mM/liter caused
a slight prolongation of both false tendon and papillary muscle action potentials, while in-
creasing K\(^+\) to 5.4 mM/liter caused a decrease
in action potential durations of both cardiac
fibers. However, in 5.4 mM/liter K\(^+\) action
potential durations (fig. 2) and functional
refractory periods (not shown) of Purkinje
fibers exceeded those of ventricular muscle
units. As illustrated in figure 3, action potential
durations of false tendon fibers still exceeded
those of papillary muscle when the K\(^+\) con-
centration was increased to 8.1 mM/liter.

When calcium was raised to 7.2 mM/liter
and K\(^+\) decreased to 0.9 mM/liter, marked
changes occurred in action potential configura-
tion of both tissues; diastolic depolarization
became prominent in false tendon fibers and
the plateau phase of the action potential de-
creased in both. There was some indication
that the differences between the refractory
periods of the two tissues might be decreased
somewhat in high Ca-low K solution. A 75% decrease in sodium (replaced by choline) re-
duced the action potential durations of both false tendon and papillary muscle fibers; but false tendon action potential durations still exceeded ventricular muscle values. Under
all of these conditions of perfusion the FRP
and APD of the false tendon cells exceeded
those of papillary muscle.

B. EFFECTS OF CHANGES IN CYCLE LENGTH

Increasing the basic driving frequency (i.e.,
decreasing the basic cycle length) shortens
the action potential duration of cardiac fibers.\(^2\)

![Figure 2](http://circres.ahajournals.org/)

Intracellular action potentials recorded simultaneously
from false tendon (above) and papillary muscle (be-
low) during perfusion with 5.4 mM/liter K\(^+\) solution.
The same preparation was used also for perfusion with
normal Tyrode's solution (fig. 4). Rate of stimula-
tion was increased from 1/sec in one to 6/sec in six.
An alternation in duration and action potential ampli-
tude in papillary muscle and false tendon cells can
be noted at rapid rates of stimulation. Calibrations
represent 100 ms and 200 msec.

*Circulation Research, Vol. XVII, September 1965*
We investigated the possibility that changes of driving frequency might exert differential effects on false tendon and papillary muscle units.

**Action Potential Duration**

The configuration and duration of false tendon and papillary muscle action potentials in normal Tyrode's solution are shown in figure 4 when the basic driving frequency was increased stepwise from 1/sec in trace 1 to 6/sec in trace 6. In trace 1 the duration of the action potential recorded from the false tendon fiber (top action potential) was nearly double the duration of the papillary muscle action potential (440 msec versus 225 msec). When the basic driving frequency was increased progressively from 1/sec to 6/sec, the APD of both tissues was decreased, but the difference between them diminished, (from 215 msec at 1/sec to 55 msec at 6/sec). The greater influence of cycle length on false
tendon action potential durations was a constant finding.

The decreased difference between durations of false tendon and papillary muscle action potentials at short cycle length is further illustrated in figure 5. In this graph, intracellular action potential duration is plotted against cycle length for 9 false tendon (triangles) and 13 papillary muscle cells (circles) recorded during a single experiment. At a cycle length of 1,000 msec a difference in duration of about 150 msec was present between false tendon and papillary muscle action potentials, while at a cycle length of 200 msec only about a 30 msec difference was present. In some experiments, at the maximum driving frequency there was no difference in APD of the two tissues.

A consistent difference was not observed between action potential durations and functional refractory periods recorded from left and right ventricular free-running false tendons. In some experiments action potential durations recorded from right ventricular free-running false tendons were 15 to 20 msec longer than left ventricular free-running false tendon action potential durations; in other experiments the opposite relationship was observed. To determine APD and FRP differences between right and left ventricular Pur
FUNCTIONAL REFRACTORY PERIOD OF CARDIAC FIBERS

Action potential durations of two right ventricular free running false tendons fibers (open squares), two left ventricular free running false tendons fibers (closed squares), two right endocardial Purkinje fibers (open circles), two left endocardial Purkinje fibers (closed circles), and two right papillary muscle fibers (open triangles) are plotted in msec at different basic cycle lengths. All units were recorded in the same experiment. At long cycle lengths, free running false tendon values exceed those of endocardial Purkinje fibers; both free running and endocardial Purkinje fiber action potential durations exceed those of papillary muscle. At short cycle lengths, however, values for Purkinje fibers and papillary muscle approach each other.

In conduction from papillary muscle to false tendon, and vice versa, small changes in the S₂S₃ interval often resulted in large changes in the response intervals of the two tissues. Because of this junctional transmission phenomenon, FRP measurements were routinely made by stimulating and recording from the same cardiac tissue at small stimulating to recording distances. Functional refractory periods were determined first at slow basic frequencies and then at progressively more rapid rates.

The false tendon and papillary muscle action potentials in figure 7, recorded in the same experiment, demonstrate the differences in duration and configuration exhibited by basic (column S₁) and premature false tendon and papillary muscle action potentials. The earliest possible premature responses elicited in false tendon and papillary muscle are shown in the second column (S₂). The intervals between responses represent the func-
Intracellular action potentials recorded from a false tendon cell (above) and a papillary muscle cell (below). The left-hand column (S₁) represents action potentials at a basic cycle length of 1000 msec. Middle column (S₂) demonstrates the FRP of false tendon and papillary muscle cells at a basic frequency of 1/sec. In the right-hand column are the functional refractory periods of the premature responses. Calibrations are 100 mv and 200 msec. Base line time dots are 100 msec apart.

Functional refractory periods. Note that the FRP of the false tendon cell (312 msec) was longer than that of the papillary muscle (208 msec) at the basic cycle length of 1,000 msec. The rate of depolarization of the false tendon premature response was much slower than that for the basic driven response and a "notch" often occurred in the rising phase of premature responses. The premature action potential response was also shorter in duration and smaller in amplitude than the normal driven beat. The premature response of papillary muscle exhibited very little decrease in the rate of depolarization or in the amplitude of the premature action potential. A greater decrease in amplitude and rate of depolarization was noted, however, in premature responses of many papillary muscle cells.

The papillary muscle cells were not usually excited as early, during repolarization, as were false tendon cells. This may be the result of the conduction distance between stimulating and recording electrodes. The FRP as recorded must be greater than the true FRP of stimulated cells by an increment in conduction time of the premature response. In the more slowly conducting ventricular muscle tissue, this error must be greater.

The right-hand column of figure 7 (S₃) illustrates the method of determining the FRP of premature beats as determined by the earliest possible second premature or S₃ response. The functional refractory periods of premature cycles of both false tendon and papillary muscle cells were shorter than for basic cycles. The rate of depolarization, action potential duration, and amplitude of the third order responses in false tendon and papillary muscle were also less than for the basic driven beat.

The relationship of the functional refractory periods of false tendon and papillary muscle at different cycle lengths is shown in...
the left graph of figure 8. Open triangles and circles denote the functional refractory periods of basic responses; closed symbols represent functional refractory periods of premature responses. The FRP values and corresponding action potential duration values shown in the right-hand graph were obtained in the same experiment. The functional refractory periods of premature responses recorded from false tendon and papillary muscle cells overlap at cycle lengths shorter than 300 msec. Therefore, at very short cycle lengths there was often no difference in the duration of the functional refractory periods of some false tendon and papillary muscle cells. In keeping with this observation, the maximum one-to-one driving frequency was often the same for papillary muscle and false tendon cells.

Figure 8 shows also that, at slow rates, false tendon cells were re-excitabale earlier during repolarization than papillary muscle units, i.e., at slow frequencies the action potential duration (right graph) and functional refractory periods of papillary muscle units (left graph) are more nearly equal than corresponding values for false tendon units.

Cumulative Effects of Cycle Length on Action Potential Duration

Strict dependence of FRP upon the immediately preceding cycle length in papillary muscle units was not always observed, as can be noted in figure 8 where a few premature functional refractory periods (closed circles) lie above the basic ones (open circles). This can be observed also in figure 12 where the functional refractory periods of basic and premature beats of papillary muscle were compared with those of epicardial units. Therefore, a cumulative effect of cycle length on FRP was present in some papillary muscle cells but absent in others. An example of a cell in which a cumulative effect was prominent is shown in figure 9A. At a basic cycle length of 1,000 msec the APD of a premature response introduced 333 msec after the last driven response was 243 msec. When the preparation was driven at a basic cycle length of 500 msec the APD of a premature response introduced 166 msec after the last driven response was 220 msec.
of 333 msec, the APD of the basic response was 216 msec. A papillary muscle cell, where no cumulative effect of cycle length on APD was observed, is shown in figure 9B. The APD of both the premature and basic response at a cycle length of 333 msec was 244 msec.

In false tendon fibers the APD of premature responses routinely was as short as that of basic responses having the same preceding cycle length. An example is shown in figure 10.

From these results it follows that under the conditions of these experiments the difference between papillary muscle and false tendon cells, although great at low frequencies, diminishes at higher driving rates and may even disappear for premature responses.

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**FIGURE 9**

A: upper trace: A papillary muscle was driven at a basic cycle length (BCL) of 1000 msec with a premature response elicited 333 msec after the basic response (second action potential). The two action potentials in the lower part of A were recorded at a basic cycle length of 333 msec: The premature action potential duration (APD) at 333 msec exceeds the APD recorded at a basic cycle length of 333 msec. B: Another papillary muscle cell recorded in a different experiment. Upper trace: A premature response was evoked at 333 msec in a basic cycle length of 1000 msec. Lower trace: The cell was driven at a basic cycle length of 333 msec. The action potential durations of the premature and basic responses are the same. Time calibration 100 msec, voltage calibration, 100 mv.

**FIGURE 10**

Action potentials above and below were recorded from the same false tendon cell. Above: a premature response elicited 333 msec after the basic response when the basic cycle length was 1000 msec. Below: an action potential recorded from the same cell at a basic cycle length of 333 msec. Calibrations: 100 mv and 200 msec. Time dots on the bottom trace are 100 msec apart.
C. REPETITIVE RESPONSES FOLLOWING PREMATURE ACTIVATION

Spontaneous activity frequently resulted from evoking one or more premature responses in either the false tendon or papillary muscle. In many instances three or more spontaneous beats occurred, while in others only a single extrasystole was observed. An example of spontaneous repetitive activity resulting from premature stimulation of false tendon (A and B) or papillary muscle (C and D) is illustrated in figure 11.

D. INTRACELLULAR RECORDINGS FROM CELLS ON THE EPICARDIAL AND ENDOCARDIAL SURFACES

The action potential duration and FRP of muscle cells on the epicardial surface (for convenience, “epicardial” cells) were compared with those of papillary muscle (“endocardial”) cells in 15 experiments. At identical cycle lengths the action potentials recorded from epicardial cells were usually shorter in duration than corresponding papillary muscle (“endocardial”) action potentials.

The data in figure 12, drawn from two experiments, show the relationship between cycle length and APD for epicardial cells (triangles) and endocardial muscle cells (circles). The difference in APD between endocardial and epicardial cells decreased as the cycle length was abbreviated. The APD of premature responses at the epicardial surface often fell above the curve relating APD to basic cycle length. This suggests that a cumulative effect of cycle length on the APD of some epicardial cells was present, as already described for papillary muscle cells.

In several experiments simultaneous intracellular recordings were obtained from endocardial and epicardial ventricular fibers. Each action potential was led into one side of a differential amplifier and the difference between the endocardial and epicardial intracellular potentials recorded simultaneously with the transmembrane potentials. Figure 13 is an example of one such experiment. The endocardial fiber was excited slightly before the epicardial unit and the differential amplifier recorded an upright depolarization deflection. Because repolarization of the epicardial cell preceded that of the endocardial fiber, the repolarization wave was also upright in the differential record. The resemblance of the differential record to the remote lead QRS-T deflection of the electrocardiogram is apparent, although it is not possible to conclude that these “epicardial”-“endocardial” APD differences are responsible for the polarity of the T wave.

Discussion

A. PAPILLARY MUSCLE AND FALSE TENDON FUNCTIONAL REFRACTORY PERIODS

The present study has shown that changes in the ionic composition of the perfusion fluid, substitution of blood or plasma for Tyrode’s solution, the effect of time lapse following removal of the cardiac preparation from the animal, addition of carbon dioxide buffer, changes in temperature of the perfusion fluid, and addition of epinephrine and acetylcholine do not differentially change false tendon and papillary muscle functional refractory periods and action potential durations. The FRP and APD of false tendon cells (Purkinje fibers) exceed those of papillary muscle under all conditions mentioned. The only variable that was found to influence differentially the functional refractory periods...
and action potential durations of false tendon and papillary muscle cells was cycle length. At very short cycle lengths produced by premature beats the FRP and the action potential duration of false tendon approach those of papillary muscle cells. In a few experiments the functional refractory periods of some premature false tendon responses were less than the corresponding values for papillary muscle.

Several factors that may alter differentially the functional refractory periods and action potential durations of the specialized conduction tissue and ventricular muscle were not studied. Two such unexplored variables are temperature gradients and differential tensions. For example, in the closed chest animal, temperature gradients exist across the myocardial wall and between the ventricular cavity and myocardium. Likewise, the various cardiac structures in situ are subjected to mechanical stresses that differ from those encountered in the isolated tissue.

B. RELATIONSHIP TO VENTRICULAR FIBRILLATION

The role played by the disparity between refractory periods of ventricular muscle and specialized conduction tissues in the genesis of, or protection against, ventricular fibrillation has been interpreted differently by different investigators. Brooks and Hoffman and Hoffman have suggested that a longer FRP in Purkinje fibers than in ventricular muscle fibers, might predispose to disorganization of impulse propagation, because an ectopic beat initiated in ventricular muscle would be forced...
FUNCTIONAL REFRACTORY PERIOD OF CARDIAC FIBERS

Transmembrane potential recorded from an endocardial ventricular muscle cell (ENDO) and one from an epicardial ventricular muscle cell (EPI) were electronically differentiated in the lower trace (DIFF). The depolarization complex was retouched.

FIGURE 13

to travel slowly in muscle before entry into the Purkinje fibers could guarantee rapid spread to the remaining portions of the ventricles. Hoffman and Cranefield2 have suggested that the difference in action potential durations may permit re-entry to occur, at least locally, at junctional points between muscle and Purkinje tissue. Re-excitation of a partially or completely repolarized muscle fiber from an adjoining and still depolarized Purkinje fiber could, conceivably, occur. This is perhaps the most likely explanation for the genesis of closely coupled premature beats, and repetition of the event could cause multiple responses or fibrillation. It is pertinent that ectopic premature beats and episodes of ventricular fibrillation in cases of complete heart block are observed more commonly when the idioventricular rate is very slow, i.e., when the disparity of refractory periods should be greatest.11

The disparity between Purkinje and ventricular muscle functional refractory periods may provide an opportunity for re-entry, and may therefore represent a potential hazard. However, it may also be argued that a relatively long FRP in the rapidly conducting tissue offers protection against fibrillation originating from premature responses conducted to ventricular muscle via the specialized conduction system. An early premature impulse initiated in or above the specialized conduction system will be propagated rapidly to the ventricular myocardium, but it will arrive after the muscle tissue is fully repolarized and therefore presumably after the expiration of the "vulnerable period." At high heart rates, of course, this protection would decrease as the functional refractory periods of muscle and specialized conduction tissue approach a common value. In fact, ventricular fibrillation can be induced simply by accelerating the frequency of driving stimuli. Furthermore, as illustrated in our experiments, premature activation can further reduce the refractory period difference between Purkinje fibers and ventricular muscle and establish the necessary conditions for initiating ventricular fibrillation. At rapid heart rates out of phase alternation in action potential duration and FRP in Purkinje and papillary muscle fibers might predispose to ventricular fibrillation by increasing inhomogeneity. Likewise, the different cumulative effects of cycle length on action potential duration and FRP in Purkinje fibers and papillary muscle may also cause disparity.

In support of the concept that a longer FRP in the conducting tissue than in the ventricular muscle may serve to reduce rather than increase the risk of fibrillation, we may cite observations made under circumstances in which the ventricular refractory period was shown to be longer than that of the conducting system. In the studies of newborn animals reported by Preston et al.,6 it was found that early atrial premature beats were propagated to the ventricles and appeared at the epicardial surface precisely at the end of the ventricular refractory period. No earlier responses could be induced by direct stimulation of the ventricles with pulses of three to five times the diastolic threshold. Clearly, neither the A-V node nor any element of the Purkinje network could have had a longer refractory
period than the muscle itself. Furthermore, the earliest possible ventricular premature beat was often propagated back to the atria at full speed, suggesting that the conducting system was not even relatively refractory at the expiration of the functional refractory period of the muscle. In such young hearts, premature atrial responses regularly caused ventricular fibrillation. These observations suggest that (1) the “vulnerable” period is of real physiological significance and (2) that the relatively brief FRP of the conducting system permitted the arrival of premature supraventricular responses during the vulnerable period of the ventricular muscle. Similar observations have been made in the hearts of adult dogs treated with a substituted propiophenone (U-0882).

C. EPICARDIAL AND ENDOCARDIAL DIFFERENCES IN ACTION POTENTIAL DURATIONS AND FUNCTIONAL REFRACTORY PERIODS

The observation that the canine epicardial cells have a shorter action potential duration and FRP than endocardial cells is consistent with the classical electrocardiographic explanation for the “upright” T wave, viz. that depolarization occurs from endocardium to epicardium and repolarization proceeds in the opposite direction. However, several problems are present in these studies. A monopolar gross electrogram was not recorded from the isolated tissue to make certain that when the epicardial cells had a shorter FRP than endocardial ventricular or endocardial Purkinje fibers, upright depolarization and upright repolarization waves were recorded. The ventricular epicardium has a considerable amount of connective tissue on its surface that may act as a barrier for diffusion. The epicardial cells frequently have a lower transmembrane resting potential and action potential than endocardial cells. Therefore, the observed differences in epicardial and endocardial APD may reflect a relative hypoxia of epicardial cells in the in vitro experiments rather than a meaningful physiologic difference.

Summary

In vitro studies have shown that alterations in the ionic composition of the perfusion fluid, substitution of blood or plasma for Tyrode’s solution, time lapse following removal of the cardiac preparation from the animal, and addition of varying amounts of acetylcholine and/or epinephrine, do not change differentially the functional refractory period and action potential duration of false tendon and papillary muscle fibers; false tendon values exceeded those of papillary muscle in all of the above conditions. Cycle length was the only variable found to influence differentially false tendon and papillary muscle functional refractory periods and action potential durations. At very short cycle lengths, produced by premature responses, the functional refractory period and action potential duration of false tendon and papillary muscle cells approached each other. In some experiments the functional refractory periods of premature false tendon responses were less than corresponding values for papillary muscle. The relationship between the action potential durations and functional refractory periods of canine epicardial and endocardial cells was investigated also. It was found that the epicardial cells had a shorter functional refractory period and action potential duration than endocardial units when studied at physiological rates.

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Durations of Transmembrane Action Potentials and Functional Refractory Periods of Canine False Tendon and Ventricular Myocardium:: Comparisons in Single Fibers
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Circ Res. 1965;17:259-273
doi: 10.1161/01.RES.17.3.259

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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