Effects of Caffeine and Ryanodine on Delayed Afterdepolarizations and Sustained Rhythmic Activity in 1-Day-Old Myocardial Infarction in the Dog

Mohamed Boutjdir, PhD, Nabil El-Sherif, MD, and William B. Gough, PhD

Caffeine and ryanodine are known to modulate oscillatory release of Ca\(^{2+}\) from the sarcoplasmic reticulum. The effects of caffeine and ryanodine on delayed afterdepolarizations (DADs) and sustained rhythmic activity in subendocardial Purkinje fibers surviving 1-day-old myocardial infarction in the dog were studied with standard microelectrode techniques. In preparations that showed sustained rhythmic activity, a high concentration of caffeine (10 mM) and ryanodine (10\(^{-7}\) and 10\(^{-6}\) M) slowed and terminated the sustained rhythmic activity and markedly suppressed DADs. An increase in the temperature of the tissue bath from 37\(^{\circ}\) to 39\(^{\circ}\) C did not change these results. In quiescent normal and infarcted preparations, a low concentration of caffeine (0.5 mM) differentially induced DADs in ischemic but not in normal Purkinje fibers, increased the amplitude of existing DADs, and brought subthreshold DADs to threshold potential that caused triggered activity. Our results are consistent with the hypothesis that triggered activity arising from DADs characterizes the sustained rhythmic activity in endocardial preparations 1 day after infarction and indicate an important role for the sarcoplasmic reticulum in the genesis of DADs and triggered activity in this model. (Circulation 1990;81:1393–1400)

Subendocardial Purkinje fibers surviving 1 day after myocardial infarction in the dog show varying degrees of partial depolarization and spontaneous rhythmic activity.\(^1\)-\(^4\) Two different mechanisms, abnormal automaticity\(^3\)-\(^7\) and triggered activity arising from a delayed afterdepolarization (DAD),\(^8\) have been proposed to account for the arrhythmia. During sustained rhythmic activity, abnormal automaticity at a reduced membrane potential will be difficult to discern from triggered activity arising from DADs. In earlier studies of 1-day-old ischemic endocardial preparations in the dog, the sustained rhythmic activity was considered the result of abnormal automaticity.\(^1\)-\(^3\) However, when the initiation and termination of these rhythms were studied in detail, most were found to be caused by triggered activity arising from DADs.\(^4\) Ischemia is known to result in an increase in [Ca\(^{2+}\)].\(^8\)-\(^10\) A model has emerged describing the ionic mechanisms responsible for DADs, and it suggests that one phenomenon is common to all preparations exhibiting DADs, that is, an increase in [Ca\(^{2+}\)].\(^1\) When [Ca\(^{2+}\)] is sufficiently high, subsequent action potentials initiate intracellular oscillatory Ca\(^{2+}\) movement presumably from the sarcoplasmic reticulum. This in turn will cause a transient inward current thought to be due to Ca\(^{2+}\) modulation of a sarcolemmal nonspecific cation conductance or a Na\(^+\)-Ca\(^{2+}\) exchange carrier.\(^12\)-\(^17\)

We have shown that Ca\(^{2+}\) channel blocking agents can suppress DAD and triggered activity in subendocardial Purkinje fibers from 1-day-old infarction in the dog.\(^4\),\(^18\),\(^19\) Similar observations were reported in preparations with digitalis toxicity.\(^12\),\(^20\) These observations are compatible with the interpretation that Ca\(^{2+}\) channel blockade by decreasing transsarcolemmal Ca\(^{2+}\) influx will result in a decrease of [Ca\(^{2+}\)], and, hence, a decrease in the transient inward current.\(^12\),\(^13\) Caffeine and ryanodine are two pharmacological probes used in the evaluation of arrhythmogenic mechanisms in which oscillatory release of Ca\(^{2+}\) from the sarcoplasmic reticulum may be involved. At a low concentration, caffeine enhances the release of Ca\(^{2+}\) from the sarcoplasmic reticulum. However, at higher concentrations, caffeine initially releases Ca\(^{2+}\) from the sarcoplasmic reticulum and then quickly inhibits the reuptake. This eventually...
depletes the sarcoplasmic reticulum of Ca\textsuperscript{2+}.\textsuperscript{21–25} Ryanodine blocks the release of Ca\textsuperscript{2+} from the sarcoplasmic reticulum,\textsuperscript{26,27} although it may induce a leak of Ca\textsuperscript{2+} from the sarcoplasmic reticulum\textsuperscript{28} resulting in depletion.\textsuperscript{29,30} Ryanodine does not interfere with transsarcolemmal Ca\textsuperscript{2+} influx by way of the slow channel or Na\textsuperscript{+}-Ca\textsuperscript{2+} exchange. In this study, we tested the hypothesis that oscillatory release of Ca\textsuperscript{2+} from the sarcoplasmic reticulum may be involved in the rhythmic activity seen in endocardial preparations from 1-day-old myocardial infarction in the dog. Furthermore, because the temperature of the superfusate of in vitro preparations was suggested to dramatically modulate the behavior of the rhythmic activity,\textsuperscript{6} experiments were conducted at two different superfusate temperatures.

Methods

Dogs weighing 14–18 kg were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and maintained with supplemental doses as required. The animal was ventilated with 100% oxygen through an endotracheal tube with a Harvard positive pressure pump. Under sterile conditions, a left thoracotomy was performed at the fourth intercostal space. The left anterior descending coronary artery was dissected, and a one-stage ligation was performed just distal to the anterior septal artery. The thorax was closed, and the animal was allowed to recover. On the following day (22–26 hours after occlusion), a left thoracotomy was again performed under sodium pentobarbital anesthesia, and the heart was removed and placed in an oxygenated, room temperature Tyrode’s solution. Endocardial preparations (4x8–8x16 mm and up to 2 mm thick) were obtained from the normal and infarcted zones of the heart and placed with the endocardial surface upward in a Plexiglas tissue bath. Special care was taken to minimize mechanical trauma to the endocardial surface during the excision and dissection. The infarcted zone on the endocardial surface appeared pale and was clearly distinguishable from the surrounding noninfarcted regions by a distinct border. For control experiments, specimens were studied from the normal endocardial surface of the left and right ventricles.

Tissue preparations were superfused with Tyrode’s solution equilibrated with 95% O\textsubscript{2}-5% C\textsubscript{2}O and having a constant temperature of 37±0.5°C. In other experiments, the studies were performed at 39±0.5°C. The Tyrode’s solution had the following composition (mM): 150.8 Na\textsuperscript{+}, 4.0 K\textsuperscript{+}, 2.7 Ca\textsuperscript{2+}, 0.5 Mg\textsuperscript{2+}, 146.1 Cl\textsuperscript{−}, 24.0 HCO\textsubscript{3}−, 1.8 H\textsubscript{2}PO\textsubscript{4}−, and 5.5 dextrose. The pH was 7.2–7.4, as measured by an ABL 1 acid-base laboratory (Radiometer, Copenhagen, Denmark).

Transmembrane action potentials were measured with glass microelectrodes filled with 3 M KCl having a resistance of 10–30 MΩ. Each microelectrode was coupled to a microprobe system (model M-707, WPI, New Haven, Connecticut) using Plexiglas holders with an integral Ag-AgCl electrode. Transmembrane potentials were continuously recorded on a two-channel chart recorder (model 220, Gould-Brush, Cleveland, Ohio). Selected photographic records of action potentials were also obtained from a storage oscilloscope (model 5111, Tektronix, Beaverton, Oregon) with a Polaroid C-59 oscilloscopic camera. Electrical stimulation of the preparation was done through bipolar platinum electrodes (Rhodes Medical Instruments, Woodland Hills, California) and a programmable stimulator (model DTU-101 MVA, Bloom Associates, Ltd, Reading, Pennsylvania). The stimuli consisted of rectangular pulses 2–5 msec long and at least two times threshold voltage. Preparations were driven for eight beats at cycle lengths between 1,000 and 200 msec in 100 msec decrements. The stimulation was then stopped for 4–9 seconds to observe any afterpotentials. The appropriate amount of caffeine (Sigma Chemical, St. Louis, Missouri) was taken from stock solution of 0.1 M dissolved in distilled water. Ryanodine (Penick, Lyndhurst, New Jersey) was prepared from stock solution of 10⁻³ M dissolved in distilled water.

Data Analysis

Data are presented as mean±SD. The amplitude of the DAD (mV) was measured from the nadir of the maximum diastolic potential to the peak of the afterdepolarization. The coupling interval (msec) was measured from the upstroke of the preceding action potential to the peak of the DAD. A paired t test was used to test the significance of drug-induced changes on the cycle length of sustained rhythmic activity and on the amplitude of DAD. The effects of different cycle lengths on the amplitude of DAD during the control period and after administration of a low concentration of caffeine were compared by analysis of variance. When significant difference between groups was detected by analysis of variance, the data were also analyzed with Scheffe’s test. A p value less than 0.05 was considered significant.

Results

Effects of High Concentration of Caffeine and Ryanodine on Sustained Rhythmic Activity at 37°C

High concentration of caffeine. In 15 infarcted preparations from eight different hearts that showed spontaneous sustained rhythmic activity, the effects of a high concentration of caffeine (10 mM) were tested. During the first minute of superfusion, the cycle length of sustained rhythm decreased. However, within 5–10 minutes, caffeine consistently increased the cycle length of the rhythmic activity before it terminated with a subthreshold DAD. Also, maximum diastolic potential decreased from a control value of −62±2 to −58±5 mV (p<0.05). During control, the mean cycle length of sustained rhythmic activity was 727±63 msec. The mean cycle length of sustained rhythmic activity before termination was 1,023±112 msec, which was significantly different from control (p<0.02). After termination, subse-
quently electrical stimulation failed to reinitiate sustained rhythmic activity, and the DADs were diminished further in amplitude. Removal of caffeine reversed these effects. The DAD gradually increased in amplitude after stimulated trains until eventually it reached threshold and gave rise to sustained rhythmic activity. Figure 1 illustrates the results from one of these experiments.

**Ryanodine.** In nine other infarcted preparations from five hearts that showed sustained rhythmic activity, the effects of two concentrations of ryanodine (10⁻⁷ M, n=4, and 10⁻⁶ M, n=5) were studied. After superfusion for 15–30 minutes, both concentrations of ryanodine increased the cycle length of sustained rhythms from 694±42 to 1,052±81 msec at 10⁻⁷ M (p<0.005) and from 710±28 to 1,210±88 msec at 10⁻⁶ M (p<0.005) before rhythmic activity terminated with a subthreshold DAD. Further superfusion of ryanodine resulted in complete suppression of DADs. Ryanodine (10⁻⁶ M) also decreased the maximum diastolic potential from -61±6 to -51±7 mV (p<0.05). The effects of ryanodine were not completely reversed after washout. Figure 2 illustrates the results from one of these experiments.

**Figure 1.** Tracings of effects of 10 mM caffeine on sustained rhythmic activity of subendocardial Purkinje fibers from 1-day-old infarct in the dog. During control, a sustained rhythm at a cycle length of 680 msec was recorded. The steady-state effect of caffeine resulted in an increase in the cycle length of the rhythmic activity to 1,050 msec before it terminated with a subthreshold delayed afterdepolarization (top panel). A sustained rhythm could not be reinitiated by subsequent stimulation (middle panel). Washout (WASH) of caffeine reversed this trend. The amplitude of the delayed afterdepolarization gradually increased before reaching threshold potential and triggered sustained activity (lower panel).

**Effects of High Concentration of Caffeine and Ryanodine on Sustained Rhythmic Activity at 39°C**

Because changes in temperature have been suggested to modify the behavior of rhythmic activity in endocardial preparations from 1-day-old infarction in the dog, we studied the effects of 10 mM caffeine and 10⁻⁶ M ryanodine on sustained rhythmic activity at 39°C. In five preparations, increasing the temperature of the tissue bath from 37°C to 39°C decreased the cycle length of sustained rhythmic activity (from 710±120 to 582±50 msec, p<0.01) and resulted in no significant change in the maximum diastolic potentials (from -62±8 to -64±6 mV). After 10 mM caffeine, the cycle length markedly increased to 1,110±105 msec (p<0.001), and maximum diastolic potential decreased to -58±8 mV (p<0.01). The effects of caffeine were reversible after washout (Figure 3). The effects of ryanodine were studied in four other preparations. An increase in the temperature of the tissue bath from 37°C to 39°C decreased the cycle length of sustained rhythmic activity (from 780±70 to 640±72 msec, p<0.05) with no significant change in the maximum diastolic potential (from -63±6 to -65±8 mV).

**Figure 2.** Tracings of effects of 10⁻⁷ M ryanodine on sustained rhythmic activity of subendocardial Purkinje fibers from 1-day-old infarct in the dog. Sustained rhythmic activity was recorded during control (left panel). Ten minutes after superfusion by ryanodine, the rate of sustained rhythmic activity slowed (middle panel) and terminated with a subthreshold delayed afterdepolarization. After 30 minutes of superfusion of ryanodine, stimulated trains failed to induce delayed afterdepolarizations or rhythmic activity (right panel). The time scale represents 1-second intervals.
mV). Ryanodine, 10⁻⁶ M, resulted in a significant lengthening of the cycle length to 1,070±90 msec (p<0.01) and a significant decrease of the maximum diastolic potential to −54±9 mV (p<0.001).

Effects of Low Concentration of Caffeine on Purkinje Fibers From Normal and Ischemic Preparations

We studied 23 ischemic endocardial preparations showing slow background automaticity (5–15 beats/min) and in which stimulated trains failed to induce fast sustained rhythmic activity. In 10 preparations, stimulated trains at cycle lengths of 1,000 to 200 msec were not followed by a discernible DAD. The effects of 0.5 mM caffeine were tested in these preparations and on normal endocardial preparations placed in the same perfusion chamber and stimulated at the same cycle lengths. Caffeine preferentially induced DADs in all ischemic preparations but in none of the normal preparations (Figure 4). The effects of caffeine were reversible on washout.

In 13 of the quiescent ischemic preparations, stimulated trains were followed by a subthreshold DAD during control. Caffeine (0.5 mM) consistently increased the amplitude of the DAD and in five of the 13 preparations, sustained triggered activity was induced (Figure 5).

Figure 6 shows the effect of 0.5 mM caffeine on the amplitude of the DAD at stimulated cycle lengths from 1,000 to 200 msec in eight preparations. During control, the amplitude of the DAD increased from 4±1.5 mV at a cycle length of 1,000 msec to 6±1.8 mV at a cycle length of 800 msec (p<0.01). The DAD amplitude decreased at shorter cycle lengths. Caffeine significantly increased the amplitude of...

FIGURE 3. Tracings of effects of 10 mM caffeine on sustained rhythmic activity at 39°C. Recordings were obtained from subendocardial Purkinje fibers from 1-day-old infarct in the dog. Panel A: Sustained rhythmic activity was recorded first at 37°C. Panel B: Temperature of the preparation was increased to 39°C, which resulted in a decrease of the cycle length of the rhythmic activity. Panel C: Superfusion of 10 mM caffeine resulted in an increase of the cycle length of the sustained rhythmic activity, which was terminated with a subthreshold delayed afterdepolarization. Note that caffeine also resulted in a significant decrease of the maximum diastolic potential and action potential amplitude of the rhythmic activity. Panel D: Sustained rhythmic activity could not be initiated by a train of eight stimuli. Panel E: During the first minutes of washout, rhythmic activity could be induced by a single stimulated action potential. The rhythmic activity gradually slowed before it terminated with a subthreshold DAD. Note the significant increase in maximum diastolic potential and action potential amplitude after washout. The time scale represents 1-second intervals.

FIGURE 4. Tracings of effects of 0.5 mM caffeine on normal and infarcted preparations. Simultaneous recordings of transmembrane potentials from normal and infarcted preparations are shown. Cells were stimulated at 900 msec (upper panel) and at 400 msec (lower panel). Only the last four action potentials of eight-beat stimulated trains are shown. During control, neither normal (top) nor infarcted (bottom) action potentials showed a delayed afterdepolarization. Within 10 minutes of superfusion of 0.5 mM caffeine, only the infarcted but not the normal cell showed a delayed afterdepolarization. Washout of the caffeine reversed this effect.
DAD at all cycle lengths tested \((p<0.05)\) but did not change its cycle length dependence.

In eight ischemic preparations showing sustained rhythmic activity (0.5 mM) caffeine significantly decreased the cycle length from 797±87 to 635±86 msec \((p<0.05)\) (Figure 7).

**Discussion**

In the present study, a low concentration of caffeine (0.5 mM) selectively induced DADs in ischemic but not in normal Purkinje fibers. It also increased the amplitude of existing DADs at all cycle lengths studied and brought subthreshold DADs to threshold potential, thereby initiating triggered activity. The low concentration of caffeine did not alter the relation of DAD amplitude to cycle length that was shown previously. In preparations showing sustained rhythmic activity, a low concentration of caffeine increased the rate of such activity. On the other hand, a high concentration of caffeine (10 mM) or ryanodine \((10^{-7} \text{ and } 10^{-6} \text{ M})\) consistently slowed and terminated sustained rhythmic activity and suppressed DADs. These results are consistent with the known effects of caffeine and ryanodine on the release and uptake of \(\text{Ca}^{2+}\) from sarcoplasmic reticulum.

Caffeine has induced a transient inward current in cultured cardiac cells. Low concentrations of caffeine have been shown to increase the amplitude of the DAD and to cause triggered activity in normal Purkinje fibers, in digitalis toxicity in Purkinje fibers, in Purkinje fibers in the presence of high \(\text{Ca}^{2+}\) and in canine coronary sinus in the presence of catecholamines. The concentration of caffeine that was reported to induce DADs in normal Purkinje fibers was 1.5–3 mM. In the present study, a lower concentration of caffeine (0.5 mM) failed to induce DADs in normal Purkinje fibers but induced DADs in ischemic Purkinje fibers. The increased sensitivity of ischemic Purkinje fibers to a low concentration of caffeine could be explained by increased \([\text{Ca}^{2+}]\), in these fibers. One the other hand, high concentrations of caffeine have been shown to abolish transient depolarizations in isolated ventricular cells, the oscillatory current in cardiac Purkinje fibers, and DADs in canine coronary sinus in the presence of catecholamines. Ryanodine has prevented transient inward current and afterpotentials in guinea pig papillary muscle and calf Purkinje fibers subjected to \(\text{Ca}^{2+}\) overload. Ryanodine and caffeine have abolished DADs and ventricular arrhythmias associated with digitalis toxicity. The close similarity between the reported effects of caffeine and ryanodine and the findings in the present study strongly suggests that sustained rhythmic activity in endocardial preparations from 1-day-old infarction in the dog is due to triggered activity arising from a
DAD rather than a manifestation of abnormal automaticity at reduced membrane potential.

The effects of ryanodine and high concentrations of caffeine cannot be ascribed to the decrease in diastolic potential that was observed with both drugs. In a recent study in ischemic Purkinje fibers, similar to the study of Ferrier in digitalis toxic Purkinje fibers, we showed that DAD amplitude depends on diastolic potential. In preparations showing sustained activity, hyperpolarizing current produced subthreshold DADs and then quiescence. On the other hand, in quiescent preparations, depolarizing current increased DAD amplitude after a train of stimulated beats. Sufficient depolarization permitted nonsustained triggered activity. (Abnormal automaticity was excluded because an identical degree of depolarization, without a previous train of stimuli, failed to induce DAD or sustained rhythmic activity.) Further depolarization during nonsustained triggered activity caused a more sustained triggered activity. Our study suggests that one need not invoke a separate, intrinsically oscillating mechanism, such as abnormal automaticity, to explain the existence of sustained in comparison with nonsustained rhythms in the same heart or isolated preparation 1 day after infarction.

Some investigators have used a matrix of drugs that have different effects on the different arrhythmogenic mechanisms to identify the electrophysiological mechanism of sustained rhythmic activity in canine endocardial preparations 1 day after infarction. This approach could be limited by the fact that most drugs act by more than one mechanism and that different concentrations of drugs can have varying effects. On the other hand, caffeine and ryanodine are specific modulators of oscillatory Ca\(^{2+}\) release from the sarcoplasmic reticulum, and as such, they are more likely to identify arrhythmogenic mechanisms that depend on [Ca\(^{2+}\)], oscillation compared with indirect modulators of [Ca\(^{2+}\)], like lidocaine, ethmozin, and doxorubicin. However, although the relation of DADs to oscillatory release of Ca\(^{2+}\) from the sarcoplasmic reticulum is reasonably well defined, the ionic mechanisms underlying abnormal automaticity at reduced membrane potential are less well understood. There is some evidence that abnormal automaticity may also involve modulation of Ca\(^{2+}\) release from the sarcoplasmic reticulum. In single cardiac myocytes, the synchronous occurrence of spontaneous localized Ca\(^{2+}\) release from the sarcoplasmic reticulum can generate "abnormal automaticity" even at a normal resting membrane potential. Ryanodine was reported to markedly slow but not abolish sustained activity in dilated human atria. This activity was called abnormal automaticity, but it showed distinct early and late phases of diastolic depolarization unlike the spontaneous infarcted endocardial preparations studied here. Because ryanodine reduced the late diastolic slope, a nonoscillatory role of [Ca\(^{2+}\)], that is, an abnormal prolongation of the [Ca\(^{2+}\)] transient, was proposed for this abnormal automaticity. Our results showing termination of sustained activity by ryanodine are consistent with the action of ryanodine on an oscillatory role of [Ca\(^{2+}\)], transient. It should be emphasized, however, that in the absence of studies that directly demonstrate that DAD and triggered activity in ischemic Purkinje fibers are the results of a transient inward current as was shown in other preparations, the arguments for triggered activity compared with abnormal automaticity cannot be definitely resolved.

The argument has been made that endocardial preparations from 1-day-old infarction in dogs demonstrate triggered activity arising from DADs at 36°C, whereas abnormal automaticity may become operative when the temperature is increased to 39°C. The ionic mechanism responsible for such a dramatic shift in the arrhythmogenic mechanism is not clear. In the present study, raising the temperature of the tissue bath from 37° to 39°C accelerated the rate of sustained rhythmic activity. However, these rhythms could still be suppressed by a high concentration of caffeine or ryanodine. Thus, our data suggest that increasing the temperature of the
tissue bath enhanced the ionic mechanism underlying DADs and triggered activity rather than causing a shift from triggered activity to abnormal automaticity. Our results are consistent with previous studies showing significant modulation of oscillatory afterpotentials with temperature.48

Although our findings strongly suggest that triggered activity arising from a DAD is the mechanism of sustained rhythmic activity seen in endocardial preparations from 1-day-old infarction in the dog, the mechanism of the spontaneous ventricular rhythms seen in vivo at the same time cannot be established with certainty. It is reasonable to assume that the same mechanism demonstrated in vitro is also operative in vivo. However, the rate of the in vivo rhythms is considerably faster than the in vitro activity. This could be explained by the effects of the sympathoadrenal system in vivo6,6 and the higher temperature of the intact animal, approximately 39°C (2–3°C higher than the temperature routinely maintained in the tissue bath).6

The influence of an intact sympathoadrenal system on the spontaneous rhythms in vivo in 1-day-old infarction is illustrated by the varying response of the in vitro and in vivo rhythms to agents that block the slow inward current. In vitro, these agents consistently terminate the sustained rhythmic activity either by suppressing the DAD and triggered activity or by inducing exit block around the site of rhythmic activity.4,18,19 On the other hand, agents that block the slow inward current are usually unsuccessful alone in suppressing the in vivo rhythm. However, in combination with β-adrenergic blocking agents, the spontaneous ventricular rhythms could be completely suppressed.49,50 The suppression of the in vivo rhythms by ethmozin and doxorubicin but not by therapeutic doses of lidocaine has been taken as evidence that abnormal automaticity and not triggered activity is the underlying mechanism.6,7 As shown from the experience with agents that block the slow inward current, these conclusions may not be warranted. Furthermore, our recent study showed that the transition from threshold to subthreshold DAD and vice versa can be only a 1-mV change in diastolic potential.44 The study suggests that DADs may become sufficiently suprathreshold so that interventions, such as overdrive pacing,6 change in temperature,6 or pharmacological inhibitors,7 may be unable to render these DADs subthreshold and thereby terminate sustained triggered activity.44

An important limitation of some studies of the effects of antiarrhythmic drugs on in vivo ventricular rhythms in 1-day-old infarction in the dog is the fact that the sinus rhythm was usually left unperturbed.7,51 It is well known that the rate of spontaneous ectopic rhythms is usually within 10 beats/min of the sinus rhythm and that the ectopic rhythms are easily overdriven by a slight acceleration of the sinus rhythm.51 Thus, a drug-induced moderate slowing of the rate of ectopic rhythms without slowing the rate of the sinus rhythm could be misinterpreted as a suppression of the ectopic rhythm by the drug. A more accurate protocol would require either consistent suppression of the sinus rhythm by vagal stimulation51 or the induction of complete atrioventricular block.52

Our observation that a low concentration of caffeine (0.5 mM) can preferentially induce or enhance DADs and triggered activity in ischemic compared with normal Purkinje fibers may have clinical implications. Clinical studies of the effects of caffeine on electrical instability and arrhythmogenesis are inconclusive.53–55 A cup of coffee usually results in the equivalent of only a 0.01–0.02 mM concentration.48 On the other hand, caffeine also results in an increase of plasma catecholamines that can potentiate its effects on DADs.56 Heavy caffeine consumption may be more effective in inducing arrhythmia in patients with conditions that already favor the induction of DADs and triggered activity such as myocardial ischemia.36

In summary, the effects of caffeine and ryanodine on rhythmic activity in endocardial preparations from 1-day-old infarction in the dog are consistent with the hypothesis that triggered activity arising from a DAD is the underlying mechanism. Our results underscore the role of oscillatory release of Ca2+ from the sarcoplasmic reticulum in the genesis of this activity.

Acknowledgments

We thank Celvin Williams for his excellent experimental assistance. We also gratefully acknowledge Ivonne Colonna for preparation of the manuscript.

References

3. Friedman PL, Stewart JR, Wit AL: Spontaneous and induced cardiac arrhythmias in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. Circ Res 1973;33:612–625
8. Schwartz A, Wood JM, Allen JC, Bornet E, Entman ML, Goldstein MA, Sordahl LZ, Suzuki M, Lewis RM: Biochemical and morphologic correlates of cardiac ischemia: I. Membrane systems. Am J Cardiol 1973;32:46–61
23. Endo M: Calcium release from the sarcoplasmic reticulum. Physiol Rev 1975;57:1–108
27. Marban E, Wier WG: Ryanodine as a tool to determine the contributions of calcium entry and calcium release to the calcium transient and contraction of cardiac Purkinje fibers. Circ Res 1985;56:133–138
45. Ferrier GR: Effects of transmembrane potential on oscillatory afterpotentials induced by acetylchlorophatidin in canine ventricular tissue. J Pharmacol Exp Ther 1980;215:332–341
47. Escande D, Coraboeuf E, Planche C: Abnormal pacemaking is modulated by sarcoplasmic reticulum in partially-depolarized myocardium from dilated right atria in humans. J Mol Cell Cardiol 1987;19:231–241
54. Myers MG, Harris L, Leenen FHH, Grant DM: Caffeine as a possible cause of ventricular arrhythmias during the healing phase of acute myocardial infarction. Am J Cardiol 1987; 59:1024–1028

KEY WORDS • triggered activity • abnormal automaticity • myocardial ischemia • sarcoplasmic reticulum
Effects of caffeine and ryanodine on delayed afterdepolarizations and sustained rhythmic activity in 1-day-old myocardial infarction in the dog.
M Boutjdir, N el-Sherif and W B Gough

Circulation. 1990;81:1393-1400
doi: 10.1161/01.CIR.81.4.1393

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/81/4/1393

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/