The Effects of Adriamycin on Normal and Ouabain-Toxic Canine Purkinje and Ventricular Muscle Fibers

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SUMMARY. In the "Na+ lag hypothesis" of cardiac glycoside action, \([\text{Ca}^{++}]\) increases through sodium-calcium exchange following block of the sodium-calcium ATPase. This accumulation of \([\text{Ca}^{++}]\) has been suggested to be responsible for digitalis-induced delayed afterdepolarizations and arrhythmias. We used standard microelectrode techniques to study the effects of adriamycin, 10-200 \(\mu\text{M}\), on the canine Purkinje fiber transmembrane potential. Adriamycin, 10 and 50 \(\mu\text{M}\), had no effect on the action potential other than inducing a 28% increase in duration at 50 \(\mu\text{M}\) \((p < 0.01)\). Adriamycin, 100 and 200 \(\mu\text{M}\), further prolonged action potential duration and decreased amplitude and \(V_{\text{max}}\). We then studied the effects of adriamycin, 50 \(\mu\text{M}\) (a concentration that purportedly blocks sodium-calcium exchange), on ouabain-induced delayed afterdepolarizations and aftercontractions in Purkinje fiber and ventricular muscle. After initially increasing delayed afterdepolarization amplitude in five of nine Purkinje fibers, adriamycin reversibly reduced their amplitude in all nine, by 78%, at a drive cycle length of 500 msec \((P < 0.01)\). Adriamycin, 50 \(\mu\text{M}\), had no effect on calcium ion-induced slow response action potentials, suggesting this concentration does not significantly reduce the slow inward current. In ventricular muscle, adriamycin, 50 \(\mu\text{M}\), did not significantly reduce contraction but did depress aftercontractions \((P < 0.025)\). In sum: in concentrations that have no effect on the AP other than prolonging duration, adriamycin, 50 \(\mu\text{M}\), reversibly depresses ouabain-induced delayed afterdepolarizations and aftercontractions; however, adriamycin, 50 \(\mu\text{M}\), does not depress calcium ion-dependent action potentials. Although the action of adriamycin on delayed afterdepolarizations and aftercontractions is consistent with direct inhibition of the transient inward current and/or an indirect reduction via reduced activity of sodium-calcium exchange, whether either or both of these mechanisms is involved must be defined by further experimentation. (Circ Res 53: 655-662, 1983)

ALTHOUGH the major use of the anthracycline antibiotic, adriamycin, is as an antineoplastic agent, acting via inhibition of DNA synthesis (Formelli et al., 1978), a major side effect is an irreversible cardiomyopathy that occurs when the cumulative dose exceeds 500-550 mg/m² body surface area (Letrak et al., 1973). Adriamycin toxicity also induces ECG abnormalities (Tan et al., 1973), including atrial and ventricular dysrhythmias (Cortes et al., 1975; Kehoe et al., 1978). Studies of the mechanisms responsible for the cardiac effects of adriamycin have shown it to inhibit calcium uptake by mitochondria (Bachman and Zbinden, 1979; Moore et al., 1977). More recently, Caroni et al. (1981) demonstrated that low concentrations of adriamycin (~40 \(\mu\text{M}\)) markedly inhibit the Na+-Ca++ exchange in isolated dog heart sarcolemmal vesicles. Because of its action on the Na+-Ca++ exchange, we viewed adriamycin as a potentially useful agent in studying the cardiac arrhythmogenic effects of digitalis. Therefore, the purpose of the present study was to test the effects of adriamycin on ouabain-induced delayed afterdepolarizations and aftercontractions. Delayed afterdepolarizations induce tachyarrhythmias in digitalis-toxic isolated cardiac fibers (e.g., Rosen and Danilo, 1980) and are also suggested to be a cause of arrhythmias in humans and in experimental animals (Rosen et al., 1980; Zipes et al., 1974).

Methods

We studied right ventricular trabecular muscles from 3-month-old beagles, and Purkinje fibers from adult mongrels and beagles. The dogs were anesthetized with pentobarbital sodium, 30 mg/kg, iv; the hearts were rapidly removed and Purkinje fiber bundles or trabecular muscles were excised and placed in iced Tyrode's solution. The preparations were superfused at a rate of 11 ml/min with Tyrode's solution gassed with 95% O2-5% CO2 and warmed to 36-37°C. The Tyrode's solution contained \((\text{mM}):\) NaCl, 131; NaHCO3, 18; NaH2PO4, 1.8; MgCl2, 0.5; CaCl2, 2.7; dextrose, 5.5; and KCl, 4.0.

The tissue bath was connected to ground, using a salt bridge and silver-silver chloride junction. The preparations were superfused at a rate of 11 ml/min with Tyrode's solution gassed with 95% O2-5% CO2 and warmed to 36-37°C. The Tyrode's solution contained \((\text{mM}):\) NaCl, 131; NaHCO3, 18; NaH2PO4, 1.8; MgCl2, 0.5; CaCl2, 2.7; dextrose, 5.5; and KCl, 4.0.
preparation were tied by silk thread to a fine gold chain. The preparations were mounted horizontally in a Lucite tissue bath having a volume of 6 ml, and studied as previously discussed (Rosen et al., 1973). One end of the preparation was attached to a Statham UC-2 force transducer and the other end to a stainless steel post affixed to a movable mount. This mount was controlled by a micro-manipulator, thereby enabling us to change the length of the preparations. In these experiments, the preparations were stimulated at a basic cycle length of 3 seconds and were studied at the peak of their length-tension curve. The output of the force transducer was carried through a Gould transducer coupler to a Gould 220 recorder. The diameters of the preparations were measured using a graticule placed in the dissecting microscope. We used the measurements of diameter to express muscle contraction as g/mm².

In electrophysiological studies, Purkinje fibers were impaled with 3 m KCl-filled glass capillary microelectrodes with tip resistances of 10–20 MΩ. In recording the transmembrane potentials, an Ag/AgCl junction was used to carry the signal to an amplifier having a high input impedance and capacity neutralization. The signals were displayed on a Tektronix oscilloscope and a Gould strip chart recorder. The records were photographed from the oscilloscope and analyzed for the following parameters, by previously described methods (Rosen et al., 1973): action potential amplitude, maximum upstroke velocity of phase 0 depolarization (Vmax), maximum diastolic potential (MDP), action potential duration at 50% repolarization (APD50), and 100% repolarization (APD100). In these experiments, the preparations were stimulated at a basic cycle length of 500 msec.

Delayed afterdepolarizations and aftercontractions were induced by superfusion with ouabain (2 × 10⁻⁷ M). In Purkinje fibers, delayed afterdepolarizations were induced after 30–40 minutes of ouabain superfusion and, in ventricular muscle, aftercontractions were induced after 60–90 minutes of ouabain superfusion.

To study the effects of adriamycin on ouabain-induced electrophysiological and mechanical changes, we discontinued ouabain and added adriamycin to the superfusate. We previously have shown that, on discontinuation of ouabain, the toxic changes in transmembrane potential persist and are stable for 60 minutes before they begin to wash out (Miura and Rosen, 1978). In three preliminary experiments, we showed that this holds true for aftercontractions, as well. This permitted us 60 minutes to observe and then wash out the effects of adriamycin in the present experiments.

For determination of delayed afterdepolarization and aftercontraction amplitudes and their coupling intervals at various drive cycle lengths, the following method was used: the basic drive cycle length was interrupted and a train of 20 pulses at the test cycle length was delivered to the preparation. This was followed by a short pause. In the experiments on contractility, the basic cycle length was three seconds, and this was maintained between test trains until active force returned to the pre-train value (2–4 minutes). In the electrophysiological experiments, the basic cycle length was 500 msec, and this was maintained for 2–3 minutes between different test trains. The aftercontractions and the transmembrane potentials were recorded at high gains on a Gould strip chart recorder and analyzed for amplitude and coupling interval according to previously described methods (Rosen and Danilo, 1980).

In those experiments in which we studied slow response action potentials in Purkinje fibers, Na⁺ was replaced by tetraethylammonium (TEA) chloride (Cranefield and Aronson, 1974). The Na⁺-free Tyrode’s contained (mM): TEA Cl, 128; Tris buffer, 5; KCl, 2.7; CaCl2, 1.62; MgCl2, 0.5; and dextrose, 5.5. The pH was adjusted to 7.5 with 5 N HCl. Here, the preparations were stimulated at a basic cycle length of 4 seconds. The maximum upstroke velocity of the slow response was measured directly from the transmembrane potential trace recorded at a rapid oscilloscope sweep speed.

In all experiments, after we placed the preparations in the tissue bath, they were permitted to equilibrate for 60 minutes in Tyrode’s solution before any drug protocol was started. Adriamycin (kindly supplied by Dr. William Perkins, Adria Laboratories Inc., Columbus, Ohio) was dissolved in Tyrode’s to make final concentrations of 10, 50, 100, and 200 μM.

Data Analysis

For all experiments, statistical analyses were performed on the raw data. Where the effect of a pharmacological treatment was tested, ANOVA was used and, when appropriate, Scheffe’s test (Snedecor and Cochran, 1980). The level of statistical significance was P < 0.05.

Results

Effects of Adriamycin on the Purkinje Fiber Transmembrane Potential

We first studied the effects of adriamycin on the transmembrane potentials of Purkinje fiber bundles superfused with Tyrode’s solution. The results are summarized in Figure 1 and a representative experiment is shown in Figure 2. None of the transmembrane potential characteristics was modified significantly by adriamycin, 10 and 50 μM. At higher adriamycin concentrations, there were concentration-related decreases in action potential amplitude and Vmax, and an increase in duration. Once these effects occurred, they were not reversible on superfusion with drug-free Tyrode’s for 30–60 minutes. Moreover, APD100 continued to increase during the wash. Finally, the effects of adriamycin were not altered by changing drive cycle length from 1200 to 500 msec.

Effects of Adriamycin on Ouabain-Pretreated Purkinje Fibers

Because adriamycin, 40 μM, inhibits Na⁺-Ca++ exchange by 80% in canine sarcolemmal vesicles (Caroni et al., 1981), and because adriamycin, 50 μM, has no significant effect on the transmembrane potential, we used 50 μM as the concentration to study the effects of adriamycin on ouabain-induced delayed afterdepolarizations.

Figure 3 shows transmembrane potentials from one experiment. Adriamycin initially increased (8 minutes) and then decreased (25 minutes) the amplitude of the delayed afterdepolarizations in the ouabain-toxic fibers. The initial increase in the delayed afterdepolarization amplitude occurred in five of nine experiments and was not statistically significant. The decrease in amplitude occurred in all experiments. It was significant and was partially...
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FIGURE 1. The effects of adriamycin on Purkinje fiber transmembrane potentials. Panel A: drive cycle length = 1200 msec. Panel B: drive cycle length = 500 msec. Abbreviations: amplitude = action potential amplitude; MDP = maximum diastolic potential; V_{\text{max}} = maximum upstroke velocity of phase 0 depolarization; APD_{50} = action potential duration at 50% repolarization. APD_{100} = action potential duration at 100% repolarization. C = control in Tyrode's. 10, 50, 100, and 200 = adriamycin concentration in \mu M. W = wash in Tyrode's. Each adriamycin concentration and the Tyrode's (W) were superfused for 30 minutes. • = P < 0.005; * = P < 0.01; A = P < 0.05 compared to control. Results expressed as mean ± SE for nine experiments.

Effects of Adriamycin on Slow Response Action Potentials in Purkinje Fibers

Prior studies have suggested that adriamycin might act, in part, by depressing the slow inward

reversible after 30 minutes in drug-free Tyrode's. The results of nine experiments on the effects of adriamycin on delayed afterdepolarization amplitude and coupling interval are shown in Figure 4. At 25 minutes, adriamycin significantly decreased delayed afterdepolarization amplitudes at all cycle lengths. This effect was greater for delayed afterdepolarizations elicited at short cycle lengths, resulting in a greater depression of the curve at short than at long drive cycles. This effect was partially reversible after 30 minutes of superfusion with Tyrode's. The relationship of delayed afterdepolarization coupling interval to drive cycle length is shown in Figure 4B. This was not altered by adriamycin.

During these experiments we also studied the effects of adriamycin, 50 \mu M, on ouabain-induced changes in the action potential. Adriamycin prolonged action potential duration significantly. It also increased action potential amplitude, an effect that occurred as delayed afterdepolarization amplitude decreased.

FIGURE 2. The effect of graded concentrations of adriamycin on the Purkinje fiber action potential. The records show the action potential in Tyrode's and in 10, 50, 100, and 200 \mu M adriamycin (after 30 minutes of superfusion at each concentration). The upper traces show a 0 potential and the transmembrane potential. The lower trace shows a 200 V/sec calibration and the electronically differentiated V_{\text{max}} of phase 0. Drive cycle length = 500 msec.

FIGURE 3. The effect of adriamycin on ouabain-induced delayed afterdepolarizations in a Purkinje fiber. The records show the transmembrane potential after 30 minutes of superfusion with ouabain, 2 \times 10^{-7} \text{M} after 8 and 25 minutes of superfusion with adriamycin, 50 \mu M and after 30 minutes of drug-free Tyrode's. Drive cycle length = 600 msec.
Effects of Adriamycin on Ventricular Muscle Contractility and on Ouabain-Induced Aftercontractions

The effects of 50 and 100 μM adriamycin on active tension of ventricular trabeculae superfused with drug-free Tyrode's solution are shown in Figure 6. The curves were not significantly different. We then studied the effects of adriamycin, 50 μM, on ouabain-induced aftercontractions in ventricular muscle. Records from a representative experiment are shown in Figure 7. Adriamycin abolished the aftercontractions at both cycle lengths; this effect was partially reversible after 30 minutes of washout. Note that the concentration of adriamycin that abolished the aftercontractions only minimally reduced twitch amplitude; moreover, during the wash, aftercontractions reappeared, whereas twitch amplitude decreased slightly. Figure 8 summarizes 10 experiments in which we studied the effects of adriamycin on aftercontractions (panel A) and the active tension of the preceding contractions (panel B). Panel A demonstrates that aftercontraction amplitude was markedly decreased by adriamycin at all cycle lengths studied. In contrast to these results, active tension was insignificantly reduced by adriamycin.

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ouabain, 2°

FIGURE 7. The effect of adriamycin on ouabain-induced aftercontractions in ventricular muscle. Panels A and B show from left to right, the twitch (at a high and a low gain) during superfusion with control Tyrode's, ouabain, 2 x 10^{-7} M (30 minutes); adriamycin, 50 μM (30 minutes); and wash (30 minutes in Tyrode's). Panel A: drive cycle length = 700 msec; Panel B: drive cycle length = 300 msec.

Discussion

The major findings of this study are that adriamycin, 50 μM, significantly depresses ouabain-induced delayed afterdepolarizations in Purkinje fibers and aftercontractions in ventricular muscle. We must stress that these effects occur at a concentration of adriamycin (50 μM) that has no significant effect on the resting or action potential. Higher concentrations of adriamycin depress action potential amplitude and V_{max} and prolong repolarization. These effects of adriamycin have been reported previously by other investigators (Lazarus et al., 1980; Simon and Bose, 1981), and cannot be reversed by washout. Moreover, their magnitude actually increases during the course of washout. Although the basis of these effects is not known, adriamycin does bind to the contractile proteins of cardiac fibers (Lewis et al., 1982). It has been suggested that, as a result, it may have a direct effect on the biophysical properties of myofibrillar proteins. By extension of this reasoning, it may be that the effects of adriamycin >100 μM are the result of toxic and irreversible effects on cell proteins, or on the cell membrane itself, resulting, as well, in changes in intracellular ionic constituents. The lack of change of maximum diastolic potential suggests that major deterioration of the cell membrane or the metabolic processes that control membrane potential is not occurring.

We selected adriamycin, 50 μM, for further study for several reasons. First, its actions on the transmembrane potential were reversible, implying that no long-standing change in cell structure or metabolism was occurring, and, second, because this concentration was in a range that had been shown previously to depress the Na^{+}-Ca^{++} exchange (Caroni et al., 1981).

There are four mechanisms by which adriamycin might depress ouabain-induced delayed afterdepolarizations and aftercontractions: (1) by blocking the "sodium channel," (2) by blocking the "slow channel," (3) by blocking the Na^{+}-Ca^{++} exchange, and (4) by blocking the transient inward current responsible for delayed afterdepolarizations or increasing repolarizing current. Although the pharmacological studies performed do not permit a final definition of the mechanism for adriamycin's actions, they do provide a basis for the following discussion and speculation.

Block of the "Sodium Channel"

That inward sodium current has an important role in the generation of delayed afterdepolarizations (and, presumably, in the generation of aftercontractions) has been determined by pharmacological modification of the sodium channel and in voltage clamp experiments. It was shown that TTX (a specific sodium channel blocker) suppressed strophanthidin (Vassalle and Scida, 1979) and ouabain (Rosen and Danilo, 1980) -induced delayed afterdepolarizations in canine Purkinje fibers. It has been postulated that, by blocking Na^{+} entry and thereby decreasing (Na^{+})_{i}, TTX might reduce Ca^{++} accumulation via the Na^{+}-Ca^{++} exchange (Sheu et al., 1982). In this respect, it is important that TTX not only
blocks the fast inward current, which is responsible for phase 0 depolarization, but also the steady state 'window' current that contributes to the maintenance of the plateau of the action potential (Attwell et al., 1979; Colatsky, 1982). Furthermore, lidocaine, which inhibits the steady state TTX-sensitive sodium current in Purkinje fibers (Colatsky, 1982; Carmeliet and Saikawa, 1982) also suppresses ouabain-induced delayed afterdepolarizations in canine Purkinje fibers (Rosen et al., 1980).

Our results suggest that adriamycin did not depress delayed afterdepolarizations and aftercontractions by blocking the fast sodium channel. We state this because the delayed afterdepolarizations were suppressed at all cycle lengths tested (250–1000 msec), but Vmax (at cycle lengths of 500 and 1200 msec), which can be used as an indicator of the fast inward current (Hondegem, 1978; Walton and Fozzard, 1979), was not significantly depressed. One might expect that an action of adriamycin on the window current might tend to reduce delayed afterdepolarization amplitude. However, TTX, which does reduce the window current (Attwell et al., 1979), has been shown to accelerate repolarization (Coraboeuf et al., 1979) as well as reduce delayed afterdepolarization amplitude (Rosen and Danilo, 1980; Vassalle and Scida, 1979). That adriamycin probably does not depress the window current is suggested by the fact that it both increased action potential duration and did not depress the plateau (see Figs. 1 and 2). Other studies, as well, have shown that adriamycin increases action potential duration in rat papillary muscle (Lazarus et al., 1980) and in canine Purkinje fibers (Simon and Bose, 1981).

Block of the “Slow Channel”

The contribution of the slow inward current to the generation of delayed afterdepolarizations has been demonstrated clearly. Ferrier and Moe (1973) found that, in Purkinje fibers, delayed afterdepolarization amplitude increases with an increase in [Ca++]i, and decreases during exposure to Mn++ (a slow channel blocker). Rosen et al. (1974) and Rosen and Danilo (1980) found that the slow channel blockers, verapamil and AHR-2666, suppressed ouabain-induced delayed afterdepolarizations in canine Purkinje fibers. The probability that adriamycin, 50 μM, does not block the slow channel is suggested by the following: First, whereas a calcium channel blocker is expected to decrease both twitch and aftercontraction amplitudes, we found that suppression of the aftercontraction was not associated with a significant decrease in twitch amplitude. Second, slow response action potentials generated in sodium-free solutions are depressed by verapamil (Cranefield et al., 1974). In such solutions, the inward depolarizing current is carried primarily by calcium ions flowing through the slow channel. In the present study, slow response action potentials were not depressed by the same concentration of adriamycin that suppressed the delayed afterdepolarizations. (It is, of course, possible that peak iCa was reduced but inactivation of iCa prolonged. This would allow an equal or greater Ca++ entry and prolongation of the slow response with no reduction in Vmax.)

Of interest in the consideration of the role of Ca++ current here is the initial increase in delayed afterdepolarization amplitude (Fig. 3) that was observed in five of nine experiments after exposure to adriamycin. This might be explained by an initial increase in slow inward current which also was observed by Azuma et al. (1981) who showed that, in ventricular cells of isolated perfused chick hearts, adriamycin "augments the slow response, possibly by an increase in cyclic AMP levels." A positive inotropic effect of low concentrations of adriamycin was also reported in rabbit papillary muscle and left atrial preparations (van Boxtel et al., 1978). Although not presented here, in five experiments, we found adriamycin, 10 μM, to increase (nonsignificantly) the twitch amplitude of ventricular muscles in a ouabain-free superfusate.

Block of Na+-Ca++ Exchange

The Na+-Ca++ exchange system is believed to be associated with the generation of delayed afterdepolarizations and aftercontractions (Kass et al., 1978a, 1978b). It has been suggested that as the sodium pump is inhibited by ouabain, [Na+]i increases, resulting in an increase in [Ca++]i via the Na+-Ca++ exchange. Caroni et al. (1981) reported that in canine heart sarcolemmal vesicles, adriamycin, 40 μM, inhibits the initial velocity of the sarcoclemmal Na+-Ca++ exchange by 80%. Moreover, they observed that the inhibition was not of the competitive type. Their observation of inhibition of Na+-Ca++ exchange by adriamycin offers a plausible explanation for our own experimental findings of a decrease in delayed afterdepolarization and aftercontraction amplitude in the absence of any changes in the action potential or twitch, other than a prolongation of action potential duration.

Block of iCa Increase of Repolarizing Current, or Reduction of Membrane Resistance

iCa, the transient inward current, has been associated with the generation of delayed afterdepolarizations and aftercontractions. However, its ionic specificity and the channel(s) involved have not been characterized completely. At present, we cannot exclude the possibility that adriamycin blocks iCa, thereby reducing delayed afterdepolarization and aftercontraction amplitude.

There is indirect evidence that argues against the hypothesis that an effect of adriamycin on repolarizing current results in a suppression of delayed afterdepolarizations and aftercontractions. We and others (Lazarus et al., 1980; Simon and Bose, 1981) have found adriamycin to prolong repolarization. It has been suggested that the prolongation of the action potential may be caused by modification of
the calcium and/or potassium currents which are both modulators of the action potential duration (Lazarus et al., 1980; Simon and Bose, 1981). Recent studies (Henning and Wit, 1981) have shown that as action potential duration is prolonged, delayed afterdepolarizations increase in magnitude. However, despite the fact that it prolonged repolarization, adriamycin reduced the amplitude of the afterdepolarizations. Hence, it is reasonable to suggest that adriamycin does not suppress delayed afterdepolarizations via an effect on repolarizing current.

It is possible that the reduction in delayed afterdepolarization amplitude is due to a reduction in membrane slope resistance produced by 50 μM adriamycin. Under such circumstances, transient inward currents of equal magnitude would produce a smaller voltage change. One mitigating factor against this alternative is the absence of significant effects of 50 μM adriamycin on the maximum dia-stolic potential. Voltage clamp studies are underway to examine membrane slope resistance and transient inward current magnitude in the presence of adriamycin. The results of these studies should definitively argue for or against this alternative.

In conclusion, our study demonstrates that adriamycin suppresses ouabain-induced delayed afterdepolarizations and aftercontractions. The mechanisms responsible for these changes await further definition.

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