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Research Article

Conversion of Ouabain-Induced Ventricular Tachycardia in Dogs with Epicardial Lidocaine: Pharmacodynamics and Functional Effects

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Epicardial antiarrhythmic drug administration was studied as a therapeutic approach for experimental ventricular tachycardia (VT) in an open-chest dog model. Lidocaine-polyurethane matrices (28%, w/w) were formulated as a model system. Matrices were placed on the left ventricular epicardium in each of 23 anesthetized open-chest dogs with ouabain-induced VT, to evaluate effectiveness in restoring sinus rhythm. Conversion occurred in all animals treated with matrices containing 300 mg or more of lidocaine after 1.5 to 7.0 min. The matrix lidocaine content correlated linearly with the time required for conversion to sinus rhythm ($r = 0.75$, $P = 0.0002$); irrespective of matrix size the myocardial/plasma lidocaine ratio was 20.1 ± 4.2 (mean ± SD) at the time of conversion. In a separate series of five dogs without ventricular tachycardia, systolic wall thickening measured with sonomicrometers after 5 min of controlled-release lidocaine administration (500- to 1000-mg matrix lidocaine content, 7.48 ± 3.49-mg/kg dose) was only minimally diminished (−14.1%) and this effect was observed only at the site of matrix placement on the anterior-apical epicardium. In contrast, intracoronary injection of 0.3 or 1.0 mg/kg of lidocaine-HCl resulted in complete elimination of wall thickening or replacement by systolic thinning. Thus epicardial administration of lidocaine from polyurethane matrices was an effective means of treating ouabain-induced ventricular tachycardia. Regional myocardial function in the vicinity of the matrices was modified to a very limited degree, supporting the view that the matrices can be used safely, without serious risk to ventricular contractile performance.

KEY WORDS: controlled release; lidocaine; ventricular tachycardia; arrhythmia.

INTRODUCTION

Epicardial administration of antiarrhythmic agents represents a novel means of treating ventricular dysrhythmias. The working hypothesis for this approach is that epicardial administration results in higher myocardial concentrations of drug than noted after intravenous injection and, therefore, offers the opportunity to optimize efficacy, while reducing the risk of adverse effects. Our experiments utilized lidocaine as a model antiarrhythmic drug in order to test this hypothesis. Controlled-release matrices have been used successfully in previous studies unrelated to arrhythmia therapy to provide locally high concentrations of various agents. For example, diphosphonate-containing silicone rubber matrices inhibited calcification of bioprosthetic heart valve leaflets while producing no drug-related toxic effects on bone (1). Similarly, a dexamethasone-eluting controlled-release cardiac pacing lead prevented scar tissue-related elevation of pacing thresholds, without steroid-induced adverse effects (2).

Previous work from our laboratory demonstrated the feasibility of epicardial lidocaine administration by controlled release for converting ouabain-induced ventricular tachycardia to sinus rhythm in dogs (3). However, this preliminary investigation did not determine the dose–response characteristics for lidocaine administered to the epicardium: instead, only a single relatively high dose was used (3). Further, the possibility that epicardial lidocaine administration could depress cardiac function was not examined.

In the present study the pharmacologic and physiologic effects of epicardial lidocaine were studied using a polyurethane controlled release matrix. The objectives of the present experiments were (1) to study the dose–response characteristics of epicardially administered lidocaine in terms of the conversion of ouabain-induced VT to sinus rhythm and (2) to determine if any local and/or global alterations in myocardial function could be associated with this route of administration.

EXPERIMENTAL

Materials

Lidocaine-HCl (75- to 150-μm particle size) was pro-

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vided by Abbott Laboratories (Chicago, IL). Ethylmethylglycylxylidide (EMGX), a synthetic analogue of lidocaine, was obtained from Astra (Worcester, MA) for use as an internal standard. A polyurethane two-component system (Tecoflex 2-80A, Thermedics Inc., Woburn, MA) was used for preparing the matrices and ferric chloride (Fisher Inc., Fair Lawn, NJ) was used as a catalyst in the polymerization. Ouabain was obtained from Sigma (St. Louis, MO). HPLC-grade ethylacetate, acetonitrile, and triethylamine were obtained from J. T. Baker (Phillipsburg, NJ).

Lidocaine assays (see below) were carried out with a high-performance liquid chromatograph (Model 6000A, Waters Inc., Bedford, MA), which was equipped with a prepacked C18 column (particle size, 5 μm), Altex Ultrasphere-ODS, 25 cm × 4.6 mm (Beckman Inc., San Ramon, CA). Electrocardiograms were recorded on an AR6 physiologic recorder (Honeywell Inc, Wellesley, MA).

Methods

Matrix Formulation and in Vitro *Release*

Lidocaine–polyurethane matrices (3) were prepared by mixing lidocaine-HCl with Tecoflex 80A (28% lidocaine HCl/Tecoflex, w/w) using 0.21 part of the diisocyanate monomer and 0.79 part of the polyether monomer. Matrices ranged in weight from 357 mg (100 mg of lidocaine) to 4500 mg (1260 mg of lidocaine). A catalyst, 0.74 μmol of ferric chloride /g polyether, was added and the mixture was then cast and cured as a film (2-mm thickness). Polymerization was carried out at 55°C for 48 hr. *In vitro* release was carried out in triplicate at 37°C at pH 7.4 (0.05 *M* Hepes) under perfect sink conditions (3). Lidocaine release was quantitated by HPLC (see below).

Ouabain-Induced Ventricular Tachycardia

Ventricular tachycardia (VT) was induced with ouabain administration (4) in male mongrel dogs (n = 23, 10.6–17.2 kg), which had undergone a left thoracotomy and pericardiotomy under pentobarbital anesthesia (30 mg/kg). Bipolar platinum electrodes were sewn to the left atrial appendage, left ventricle, and right ventricle for electrocardiographic recording. Ouabain was administered at an initial dose of 40 μg/kg intravenously at a rate of 40 μg/min and at subsequently halved dosages until sustained ventricular tachycardia was documented on the electrocardiogram. The electrocardiographic configuration utilized standard surface limb leads (II and AVR) as well as the atrial and ventricular electrodes. Circular matrices (1- to 4-cm-diameter, 2-mm thickness) ranging in weight from 357 to 4500 mg were placed directly onto the beating left anterior epicardium, 2 cm below the bifurcation of the anterior descending and circumflex coronary arteries. The matrix–myocardial interface was stable and adequate for drug release, and thus, no external fixation was required to keep the matrix in place. In each animal, the lidocaine–polyurethane matrix was left passively in place for the time needed to convert the arrhythmia to normal sinus rhythm. When sinus rhythm reappeared, the matrix was removed at once, a peripheral venous blood sample (7 ml) was taken for lidocaine analysis, and the animal was then euthanized by intracardiac potassium chloride injection. The heart was removed and frozen at −20°C until analyzed.

Regional Function Evaluation

Regional myocardial function (without ventricular tachycardia) was assessed in seven male mongrel dogs (weight, 24.5–26.0 kg) with sonomicrometers arrayed to measure transmural wall thickness (5,6). Two pairs of sonomicrometers were implanted after performing a thoracotomy under pentobarbital anesthesia: one pair was located in the anterior–apical area and the other pair was located in the anterior-basal area, approximately 4 cm away. One crystal of each pair was inserted tangentially through the myocardium. The other crystal was sewn to the epicardium with shallow sutures after determining the position of least distance between the crystals by monitoring the signals with an oscilloscope. The signals from the ultrasonic dimension gauges were processed with a Triton (Triton Technology, San Diego, CA, Model 120) sonomicrometer. The variables analyzed were end-diastolic wall thickness, end-systolic wall thickness, systolic excursion, and percentage thickening (systolic excursion as a percentage of end-diastolic wall thickness). Following our usual conventions, end-diastole was determined as the point corresponding to the onset of the positive dP/dt signal and end-systole was defined as the point 20 msec prior to peak negative dP/dt (6).

In five animals polyurethane–lidocaine matrices containing a circular hole in the center were placed in contact with the epicardium around the anterior–apical sonomicrometers for 5 min and then removed. The matrix placement duration of 5 min was arbitrarily chosen, because it fell within the range of conversion times noted in the pharmacodynamic experiments. Three matrices containing 500 mg of lidocaine and two containing 1000 mg of lidocaine were used. Each animal was then euthanized as described above. Two additional open-chest animals received intracoronary artery lidocaine-HCl injections of either 0.3 or 1.0 mg/kg in order to compare coronary administration to epicardial administration in terms of regional function.

Lidocaine Analyses

Each polyurethane matrix was analyzed for residual lidocaine to establish net *in vivo* drug delivery. Residual matrix lidocaine extraction with refluxing methanol was carried out in a Soxhlet apparatus (4). The extract was taken up to exactly 100 ml in methanol and then assayed for lidocaine using HPLC (4). An isocratic mobile phase of 0.1 *M* sodium phosphate (pH 3.0) with 0.7% (v/v) triethylamine–acetonitrile (50:50) was run at 1.5 ml/min. The column temperature was maintained at 30°C. Absorbance was monitored at 210 nm.

Plasma lidocaine levels were determined using the following procedure: into 1 ml of plasma 50 μl of the internal standard, EMGX, was added, with 400 μl of 1 *M* sodium hydroxide and 2 ml of ethylacetate. After vortexing and centrifugation (3000 rpm), the organic layer was separated. The ethylacetate was next evaporated to dryness under vacuum and the residue was redissolved in dilute sulfuric acid (0.005 *M*). Samples (20 μl) were injected into the HPLC. Calibration curves were prepared with drug free plasma spiked with

appropriate amounts of lidocaine and extracted as just described.

Cardiac lidocaine levels were measured in myocardial specimens (typically 2 g) obtained either as samples from specific matrix locations or as aliquots of whole homogenized hearts. Specimens for analysis were weighed and then homogenized over ice in 1 ml of water with a Potter–Elvenhjem tissue grinder with a Wheaton overhead stirrer (Wheaton Instruments, Millville, NJ). Fifty microliters of the internal standard (EMGX) and 8 ml of ethylacetate were added. The mixture was then vortexed and the ethylacetate layer evaporated to dryness. The residue was redissolved (as above) and analyzed for lidocaine using the above HPLC methodology. Lidocaine recovery from myocardial samples containing known amounts was 78.7 ± 2.0%.

RESULTS

In Vitro Release

Matrices released 20% of their total lidocaine content within the first 5 min and slightly more than 40% by 20 min (Fig. 1). Thereafter, an exponentially decreasing rate was observed with nearly complete release by 1 week. Thus, during the first 5 min of release the rate of drug delivery was 11.2 mg/g of matrix per min, while between 5 and 20 min the rate was 3.7 mg/g/min and, thereafter, declined to a mean release rate of approximately 1.7 mg/g/min over the next 7 days.

Pharmacodynamics

Lidocaine–polyurethane matrix efficacy for converting ouabain-induced ventricular tachycardia to sinus rhythm was evaluated in 23 dogs. Matrices (28% lidocaine, 72% polyurethane) ranged in lidocaine content from 100 to 1260 mg. Conversion occurred in all animals treated with matrices containing 300 mg or more lidocaine after 1.5 to 7.0 min. Furthermore, matrix lidocaine content was positively correlated with time for conversion to sinus rhythm ($r = 0.75$, $P = 0.0002$) (Fig. 2). It should be noted that only matrices containing less than 300 mg of lidocaine were ineffective for converting the ventricular tachycardia, despite their being left in place for at least 30 min. Control matrices (without lidocaine) were also ineffective and ventricular tachycardia in these animals persisted for more than 1 hr.

Although increasing matrix size resulted in shorter response times for conversion of ventricular tachycardia, the myocardial lidocaine levels at the time of the return of normal sinus rhythm were quite comparable across the range of matrix sizes (see Fig. 3), as were the plasma levels. Thus, these data may reflect the minimal effective lidocaine level in the myocardium that was necessary for conversion. The cardiac/plasma lidocaine level ratios were calculated and averaged 20.1 ± 4.2 (mean ± SD), emphasizing the extent to which controlled release enhanced the local concentration of the drug in the myocardium.

The net systemic drug dosage at the time of conversion ranged from 15 to nearly 50 mg/kg (Fig. 4). However, as noted earlier, plasma levels were for the most part in the therapeutic range (Fig. 3), suggesting sequestration of the CR lidocaine in the myocardium. *In vivo* drug release from

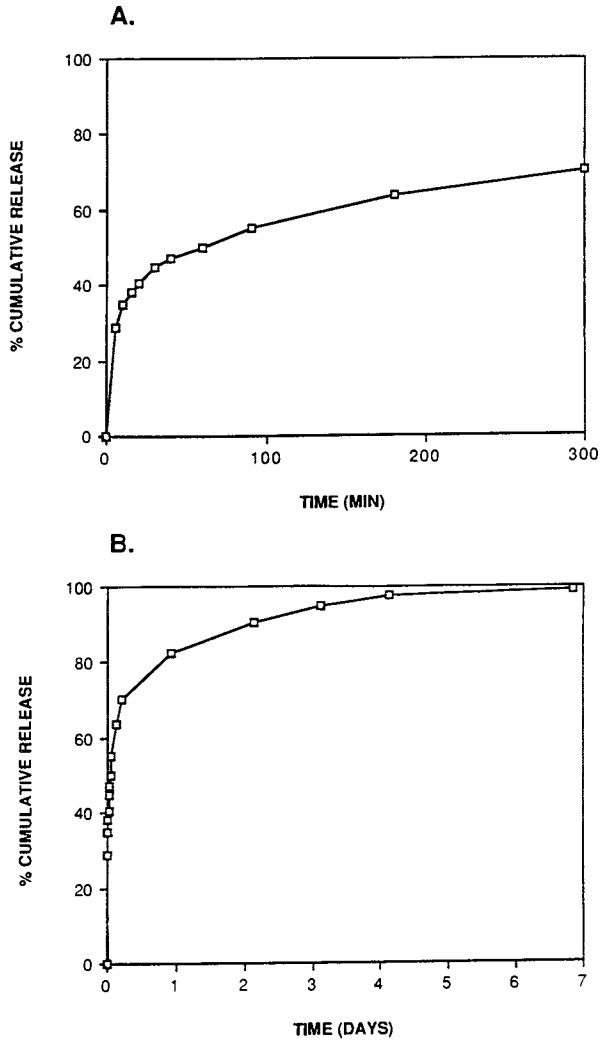

Fig. 1. *In vitro* lidocaine release from 28% polyurethane matrices at 37°C (pH 7.4). Initially rapid release rates (A) were noted to decline exponentially with matrix depletion by 7 days (B).

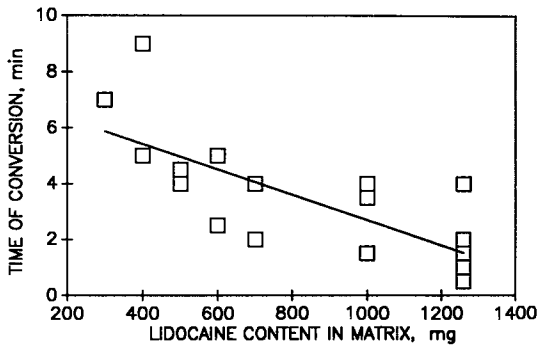

Fig. 2. Dose-response relationship of epicardial controlled-release lidocaine (28%, w/w) from polyurethane matrices. Therapeutic times indicated were required for conversion of ouabain-induced ventricular tachycardia to sinus rhythm in dogs. Matrix lidocaine content was correlated with time required for conversion to sinus rhythm ($r = 0.75$, $P = 0.0002$).

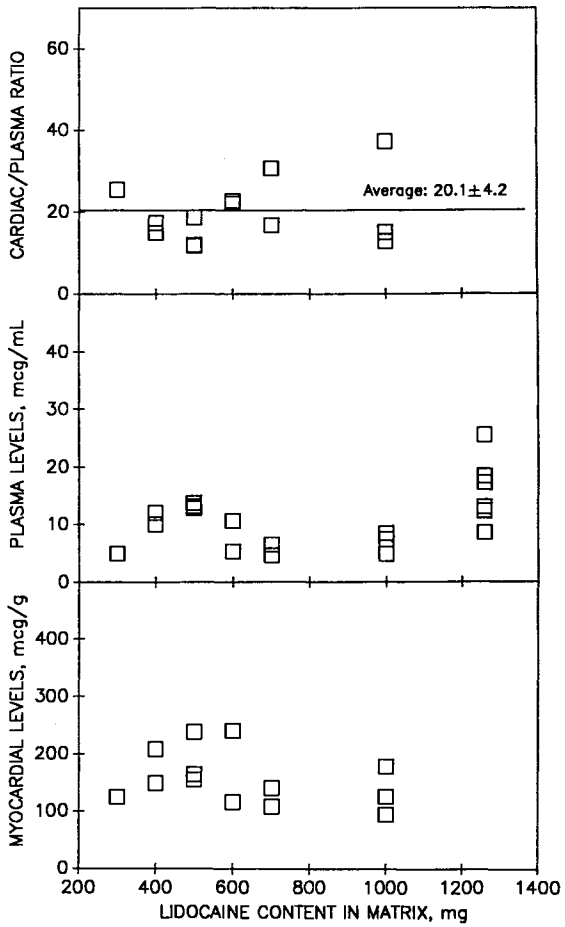

Fig. 3. Myocardial and plasma levels of epicardial controlled-release lidocaine at the time of the conversion of ouabain-induced ventricular tachycardia to sinus rhythm.

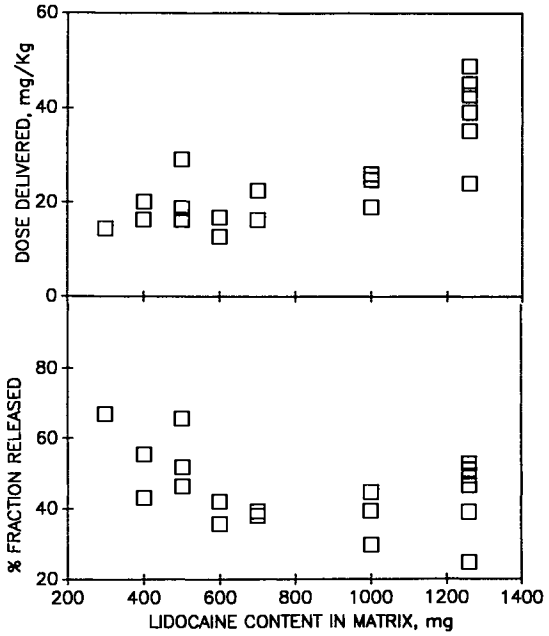

Fig. 4. *In vivo* release of lidocaine from various sizes of 28% lidocaine–polyurethane matrices during the time needed to convert ouabain-induced ventricular tachycardia to sinus rhythm in open chest dogs.

the matrices ranged from 37.9 to 66.9% of total lidocaine content by the time of conversion (Fig. 4), indicating somewhat higher level of drug delivery compared to the *in vitro* data (Fig. 1) after 1 to 7 min.

Regional Cardiac Distribution and Functional Effects

Systolic wall thickening after 5 min of controlled-release lidocaine administration decreased minimally (averaging approximately 14% from baseline) and this effect was observed only at the site of matrix placement in the anterior–apical area (Fig. 5, Table I). Nevertheless, the mean dose of lidocaine administered to these relatively larger animals was 7.48 ± 3.49 mg/kg from matrices containing 500 mg or 1000 mg of lidocaine. However, wall thickening in the basal area, approximately 4 cm from the matrix site, was characterized by an increase of about the same but opposite magnitude (averaging approximately 10% from baseline). No changes in heart rate or mean arterial blood pressure were observed.

Thus, the effects of epicardial lidocaine on regional and global left ventricular function were quite modest, despite the high dose used (Fig. 5, upper half, and Table I). To investigate this point further, intracoronary lidocaine was administered to two additional anesthetized dogs. As demonstrated dramatically in the lower portion of Fig. 5, intracoronary (left anterior descending) lidocaine (1.0 mg/kg) in one of the dogs resulted in profound depression of regional wall thickening in the apical region, in contrast to the modest change in apical wall thickening observed after epicardial administration of a greater dose (Fig. 5, upper right). In the second dog, 0.3 mg/kg of lidocaine was administered into the left circumflex coronary artery and also produced severe dyskinesia (Table I).

DISCUSSION

In previous studies, concerned with intravenous administration of lidocaine, comparable dosages to those delivered by the matrices in the present study resulted in significantly higher plasma levels (3,7) than we observed. The plasma lidocaine levels achieved with epicardial administration, however, were in the clinically effective range (8). Thus, rapid, high-level lidocaine access to the intravascular compartment can be achieved with a relatively high dosage (Fig. 4) epicardial administration, although it remains to be established if lidocaine acted locally or via rapid entry into the circulation. Preliminary results (9) using epicardial lidocaine to prevent the electrical induction of ventricular tachycardia or ventricular fibrillation have demonstrated efficacy at doses as low as 0.05 mg/kg, supporting local rather than systemic drug action, since this dose would be ineffective if it was administered intravenously.

Although the purpose of the present study was to determine the dose–response of myocardial lidocaine concentration at the time of conversion, our previous study examined the duration of antiarrhythmic activity due to the conversion dose. In these prior experiments, using matrices that contained 1200 mg of lidocaine, ventricular tachycardia recurred

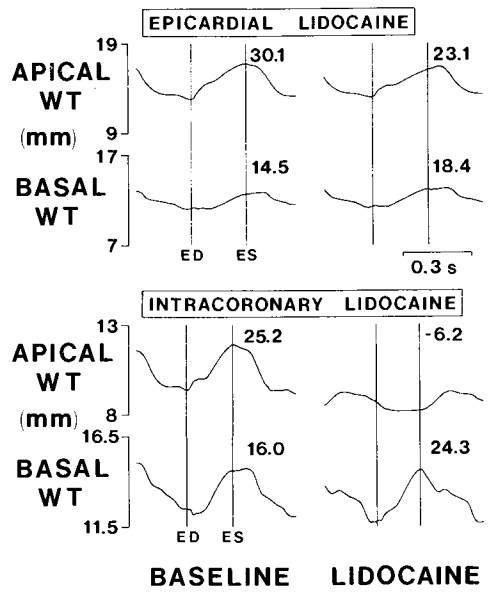

Fig. 5. Analogue tracings of wall thickness (WT) from experiments on epicardial lidocaine delivery (upper tracings) and intracoronary lidocaine administration (lower tracings). Baseline recordings are presented in the left panels; recordings after lidocaine administration are shown in the right. End-diastole (ED) and end-systole (ES) are indicated with the solid vertical lines, and percentage thickening values are superimposed on each panel. The most striking feature is the difference between epicardial and intracoronary lidocaine effects on apical wall thickening. Epicardial delivery reduced apical wall thickening modestly, whereas intracoronary administration eliminated thickening completely and replaced it with systolic thinning.

Table I. Apical Controlled-Release Lidocaine: Effects on Systolic Wall Thickening in Dogs Instrumented with Cardiac Sonomicrometers

	N	Baseline wall thickening (mm)	Post-lidocaine wall thickening (μm)	% change
Controlled-release,[a] proximal (apical) myocardium	5	2.9 ± 0.6	2.5 ± 0.6	−13.8
Controlled-release, distal (basal) myocardium	5	1.9 ± 0.2	2.1 ± 0.3	+10.5
Intracoronary artery lidocaine, 0.3 mg/kg	1			
Proximal (left circumflex)		2.10	−0.7	−33
Distal (left anterior descending)		2.40	3.45	+44
Intracoronary artery lidocaine, 1.0 mg/kg	1			
Proximal (left anterior descending)		2.0	−0.5	−25
Distal (left circumflex)		2.4	2.9	+21

[a] Matrix lidocaine content, 500 mg in three dogs and 1000 mg in two dogs; net dose delivered, 7.48 ± 3.49 mg/kg (mean ± SD), determined by analyses of matrices for residual drug.

after 15–25 min in three of the six dogs and did not recur at all in the remaining animals, which were observed for over 2 hr (3).

No attempts were made to localize arrhythmic foci via electrophysiologic mapping. Therefore, the point of origin of the ventricular tachycardia was unknown and the polymeric matrices were placed in a uniform location with the arrhythmic focus remaining unknown. Further studies employing electrophysiologic mapping techniques may demonstrate enhanced local efficacy through the use of minimally effective dosages at the site of origin of the arrhythmias or at regions of reentry.

Although intravenous lidocaine acts and is cleared from the circulation rapidly, its therapeutic use has been associated with adverse side effects, most notably depression of myocardial contractility. The mechanism of lidocaine induced cardiac dysfunction is not completely understood but may be due in part to lidocaine's inhibition of myocardial Na–K transport (10). In contrast to intravenous (or intracoronary) administration, the present results have demonstrated that controlled release of lidocaine to the epicardium produces only minimal dysfunction despite substantially elevating myocardial lidocaine levels. The epicardial dose (7.5 mg/kg) used caused only a mild local dysfunction, while profound depression was produced by as little as 0.3 mm/kg injected into a comparable regional coronary bed. The myocardial plasma lidocaine level ratios after release from epicardial matrices were significantly higher than those previously reported following intravenous administration, and the myocardial to plasma levels were greater. For example, Davis *et al.* (11) determined the plasma and myocardial concentrations of lidocaine after an intravenous bolus of 1 mg/kg in dogs; typical myocardial to plasma ratios ranged from 2.79 to 2.95. Luzzi *et al.* (12) also reported a myocardial:plasma ratio of 2.16 ± 0.45 after intravenous administration of lidocaine to dogs. In the present study, the myocardium/plasma lidocaine ratio was 20.1 ± 4.2 after epicardial administration of lidocaine. Nevertheless, only localized and quite mild myocardial dysfunction was produced, which contrasts markedly with the profound effects on function produced by direct, intracoronary administration (Fig. 4). Thus, epicardial administration of lidocaine combines therapeutic efficacy (in terms of arrhythmias) with minimization of myocardial functional depression.

The efficacy of epicardial lidocaine for treating ouabain-induced VT relates most directly to the therapy of ventricular arrhythmias due to digitalis toxicity (13). However, since this type of arrhythmia arises from triggered activity, we would expect that controlled-release lidocaine would be of benefit for the therapy of both ischemic and nonischemic ventricular arrhythmias due to this mechanism (14). Although lidocaine has also been shown to be effective for ventricular arrhythmias associated with acute myocardial ischemia (15), its clinical utility for other ventricular arrhythmias is incompletely understood. However, experimentally, lidocaine has been found to be effective for ventricular arrhythmias due to reentry (16) and lidocaine also increases the ventricular tachycardia electrical induction threshold in both the ischemic and the nonischemic myocardium (17).

Thus, epicardial lidocaine may be useful for ventricular arrhythmias in a variety of settings.

Other antiarrhythmic agents may be effective for control-release epicardial administration. In theory, any water-soluble drug would be released by the same diffusion-based mechanism as lidocaine. Preliminary studies in our laboratory have involved the successful controlled-release matrix administration of procainamide, verapamil, and amiodarone (18). In fact, amiodarone, because of its severe systemic side effects (19), would be a most suitable agent for epicardial administration.

In addition to the therapy of acute arrhythmias, controlled release of different agents from polymeric matrices may prove useful for cardiac transplant rejection, thrombolytic therapy, or congestive heart failure. In each instance, the site specific placement of a controlled-release matrix could result in enhancement of regional drug activity while reducing the likelihood of adverse side effects associated with systemic administration.

The eventual clinical utility of epicardial antiarrhythmic therapy may be realized with controlled-release matrices placed at the time of cardiac surgery. Alternatively, the endocardium could be used as the site of matrix placement via cardiac catheterization with endocardial attachment techniques. Controlled-release antiarrhythmic drug delivery systems may eventually be used as widely as other cardiovascular implants such as prosthetic valves, cardiac pacemakers, and synthetic vascular grafts. An ideal controlled-release drug delivery system for arrhythmias should have the capability of closed-loop feedback regulation of the rate of drug delivery. This is necessary in order to provide increased levels of drug when needed and to avoid toxicity. Arrhythmia detection algorithms have reached a high level of sophistication which is currently utilized in implantable defibrillator systems. Ventricular tachycardia and ventricular fibrillation detection systems are capable of triggering a modulated controlled-release system with current technology. Modulated controlled release has been achieved through either electromagnetic regulation or through the use of matrices placed in contact with a high-energy ultrasound probe. These systems may eventually be valuable for antiarrhythmic administration. Further, drug depletion would limit long-term matrix use. However, controlled-release reservoir systems with a percutaneous access port offer a potential solution to this problem by permitting replenishing or altering the drug supply.

CONCLUSION

Controlled release of lidocaine from an epicardial matrix implant in an acute dog model of ouabain-induced ventricular tachycardia acted rapidly and in a dose-dependent manner to convert ventricular tachycardia to sinus rhythm. Furthermore, this route of administration caused only minimal myocardial dysfunction that was restricted to the vicinity of the matrix.

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