Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 2612–2616, March 1995
Medical Sciences

Iontophoresis for modulation of cardiac drug delivery in dogs

(heterogeneous cation-exchange membrane/ion exchange/antiarrhythmic agents/controlled release/cardiac implant)

VINOD LABHASETWAR, THOMAS UNDERWOOD, STEVEN P. SCHWENDEMAN*, AND ROBERT J. LEVY†

Division of Pediatric Cardiology, University of Michigan, Ann Arbor, MI 48109-0576

Communicated by Robert Langer, Massachusetts Institute of Technology, Cambridge, MA, December 7, 1994

ABSTRACT **Cardiac arrhythmias are a frequent cause of death and morbidity. Conventional antiarrhythmia therapy involving oral or intravenous medication is often ineffective and complicated by drug-associated side effects. Previous studies from our laboratory have demonstrated the advantages of cardiac drug-polymer implants for enhanced efficacy for cardiac arrhythmia therapy compared with conventional administration. However, these studies were based on systems that deliver drugs at a fixed release rate. Modulation of the drug delivery rate has the advantage of regulating the amount of the drug delivered depending upon the disease state of the patient. We hypothesized that iontophoresis could be used to modulate cardiac drug delivery. In this study, we report our investigations of a cardiac drug implant in dogs that is capable of iontophoretic modulation of the administration of the antiarrhythmic agent sotalol. We used a heterogeneous cation-exchange membrane (HCM) as an electrically sensitive and highly efficient rate-limiting barrier on the cardiac-contacting surface of the implant. Thus, electric current is passed only through the HCM and not the myocardium. The iontophoretic cardiac implant demonstrated *in vitro* drug release rates that were responsive to current modulation. *In vivo* results in dogs have confirmed that iontophoresis resulted in regional coronary enhancement of sotalol levels with current-responsive increases in drug concentrations. We also observed acute current-dependent changes in ventricular effective refractory periods reflecting sotalol-induced refractoriness due to regional drug administration. In 30-day dog experiments, iontophoretic cardiac implants demonstrated robust sustained function and reproducible modulation of drug delivery kinetics.**

Cardiac arrhythmias are the cause of sudden death due to heart disease, and they complicate the long-term course of hundreds of thousands of patients on a chronic basis. At this time, conventional therapy for the prevention and treatment of cardiac arrhythmias involving oral or intravenous administration is often ineffective when the drug is given at clinically tolerable dosages, and it is frequently associated with toxic drug effects (1). Previous experimental work from our group has demonstrated the enhanced efficacy of cardiac arrhythmia therapy based on drug–polymer implants placed in direct contact with the heart. These controlled-release implants were effective on an acute and chronic basis for preventing and treating cardiac arrhythmias at lower dosages than conventional administration and were free of side effects (2–5). Regional coronary venous drug levels in these previous cardiac controlled-release studies were consistently an order of magnitude greater than simultaneous systemic levels, which were at the lower limits of detection (2–4). Furthermore, these coronary venous drug concentrations resulting from local cardiac drug delivery were in the known therapeutic range based on clinical efficacy data (2–4). However, in all of these prior investigations fixed-rate drug delivery systems were utilized. Therefore, we reasoned that modulation of the drug release kinetics of cardiac controlled-release implants would have the additional hypothetical advantage of controlling dosages depending upon arrhythmia activity. Thus, in the present study, we sought to investigate iontophoresis as a means of modulating the drug administration kinetics for antiarrhythmic agents (6). Iontophoresis may be operationally defined as the transport of charged molecules across an electrically conductive barrier with an applied current.

In this study, *dl*-sotalol hydrochloride was used as a model class III antiarrhythmic agent, contained within an epicardial reservoir implant configured with a rate-limiting heterogeneous cation-exchange membrane (HCM). Thus, sotalol transport across the HCM could be modulated by the level of transmembrane electrolytic current controlled by an external constant current source (6). When this approach is used, electrical current passes through only the HCM and not the myocardium. Prior investigations from our group have reported the successful formulation and *in vitro* characterization of an HCM-iontophoresis system (6–8). In the present studies, we investigated the hypothesis that current-responsive drug transport and current-responsive coronary circulatory drug levels would result from this iontophoretically modulated drug delivery system.

EXPERIMENTAL PROCEDURES

Materials. Silicone rubber, Silastic Q7-4840, was provided by Dow–Corning. Cation-exchange resin, Dowex 50W-2X was obtained from Sigma. *dl*-Sotalol hydrochloride was provided by Bristol–Meyers Squibb. Reagent grade sodium chloride, monobasic potassium phosphate, and dibasic potassium phosphate were purchased from Mallinckrodt.

Formulation of HCMs. The mathematical basis for the HCM implant formulation has recently been reported by our group (9). Preconditioned Dowex 50W-2X resin (53- to 75-μm particle size) was mixed with Silastic Q7-4840 (part A and part B mixed in a 1:1 ratio), at a 42% (wt/wt) loading. The resulting dispersion was cured in an aluminum mold at 80°C for 2 hr to form HCMs 620 ± 10 μm thick (mean ± SEM) as described previously (7).

Implant Design. A circular HCM of 0.27 cm^2 exposed surface area was bonded to cover the open cavity of a cylindrical silicone rubber reservoir with a 2-cm^3 fluid capacity and a Ag/AgCl anode inside, adjacent to and contacting the flat surface of the HCM, and a Ag/AgCl cathode outside the reservoir. The cathode was separated from the HCM by a silicone gasket and was further covered with a low protein binding and biocompatible Millipore membrane with a pore size of 5 μm (filter type: SV) (Fig. 1).

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: HCM, heterogeneous cation-exchange membrane; VERP, ventricular effective refractory period.

*Present address: Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139.
†To whom reprint requests should be addressed.

Downloaded at Palestinian Territory, occupied on December 19, 2021

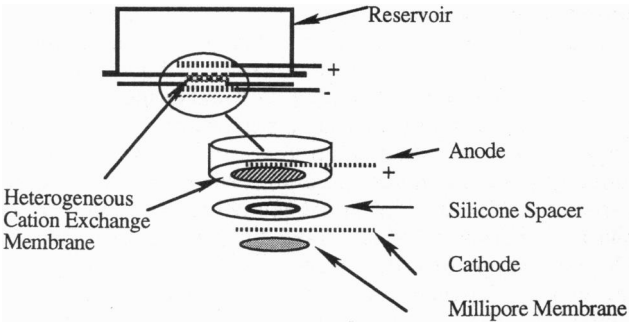

FIG. 1. Schematic representation of the cardiac iontophoretic implant.

Swelling and Conversion of the HCM to the Sotalol Form. In a typical HCM preparation, a reservoir device was equilibrated with a 0.15 M sodium chloride solution for 48 hr at 37°C for equilibrium swelling of the HCM (8). The HCM, which was in the sodium form, was next converted to the sotalol form by replacing the internal and external sodium chloride solutions with a 0.15 M *dl*-sotalol hydrochloride solution (pH = 5.24). By using a galvanostat power supply unit (University of Michigan Chemistry Shop, Ann Arbor, MI) and a Ag/AgCl electrode system (6), a constant direct current of 150 μA was passed (≈8 hr) across the HCM until the electrical potential reached a steady value (1.7 ± 0.2 V; mean ± SEM, n = 9) as determined by a Fluke multimeter (model 8062A; John Fluke Manufacturing, Everett, WA).

***In Vitro* Iontophoretic Modulation of Sotalol Release.** The HCM-iontophoretic reservoir device was filled with a fresh 0.15 M sotalol solution, and the HCM (preconditioned to the sotalol form) was first evaluated *in vitro* for modulated release of the drug at "off" and "on" currents for two and a half alternating off/on cycles. Three different current protocols were studied: protocol A, off/100 μA/off/450 μA/off; protocol B, off/450 μA/off/450 μA/off; and protocol C, off/900 μA/off/450 μA/off. Each *in vitro* study was performed with a jacketed beaker at 37°C containing Sorenson's buffer (pH 7.3) as a release medium (6). Sample aliquots were analyzed for sotalol spectrophotometrically at 227 nm with a Lambda 3B spectrophotometer (Perkin–Elmer) as previously described (3).

Acute Administration Protocols for Dogs. Male mongrel dogs (n = 9, three groups of 3) weighing 20–30 kg were used. Each animal, under halothane general anesthesia, underwent a left lateral thoracotomy through the fifth intercostal space, and the heart was suspended in a pericardial cradle. The iontophoretic device (see Fig. 1), containing 0.15 M sotalol, was sutured onto the epicardial surface of the mid-left ventricle by using 3-0 silk sutures, anchoring each suture to the circumferential silicone rubber rim of the iontophoretic reservoir device. The iontophoretic device was placed on the left ventricular epicardium just distal to the first diagonal branch of the left anterior descending (LAD) coronary artery. The iontophoresis electrodes (Ag/AgCl) from the device were connected to the external constant-current power supply unit.

For assessment of the effects of sotalol on the ventricular effective refractory period (VERP), animals were fitted with two platinum bipolar epicardial electrodes. The proximal bipolar electrodes were positioned adjacent to the apical edge of the iontophoretic implant. The other bipolar electrodes were positioned 2 cm apical from the first pair (distal electrode). The VERP was measured at 30 min from the beginning of the experiment (initial VERP) and at the end of the first (period I VERP) and second (period II VERP) iontophoretic off/on current protocols as described in our earlier publication (3). Animals were constantly monitored for spontaneous or inadvertently inducible arrhythmia activity during each stage of the acute procedures.

HCM-iontophoresis systems were used in three different dog short-term current protocols, which were comparable to the above *in vitro* protocols. After the iontophoretic device was implanted on the epicardium, no current was passed through the device for 1 hr ("off" phase); then a current of a specific amplitude was passed for 1 hr ("on" phase), depending upon the protocol used. The off and on current cycles were repeated one more time in each protocol. The three different current protocols studied reproduced the above *in vitro* protocols: protocol A, off/100 μA/off/450 μA; protocol B, off/450 μA/off/450 μA; and protocol C, off/900 μA/off/450 μA.

Blood samples for measuring sotalol levels were taken simultaneously from the external jugular vein and the largest possible branch of the great coronary vein proximal to the iontophoretic implant by using an indwelling catheter. Peripheral and coronary venous blood samples were taken every 20 min after implantation to quantitate drug levels. Plasma sotalol levels were determined by a series of procedures involving solid-phase extraction followed by HPLC separation with fluorescent detection (excitation 235 nm, emission 320 nm) with detection limits of 10 ng/ml as previously reported (3).

Chronic Administration Protocols for Dogs. In chronic (n = 9) experiments a thoracotomy was performed on dogs under halothane anesthesia as above. The pericardium was incised and an ethylene oxide-sterilized HCM-silicone reservoir device, which contained a filter-sterilized (type, acetate; pore size, 0.22 μm; Micron Separations, Westboro, MA) sotalol solution (0.15 M), was sewn to the left ventricular epicardium (as described above) under sterile conditions. Electrical leads for the iontophoretic electrodes were passed through the fifth intercostal space and positioned subcutaneously ventrodorsally. After the reservoir was secured with 2-0 Ethibond (Ethicon, Somerville, NJ), epicardial sutures were anchored to the perimeter of the silicone rim (see above). The pericardium was left open, and the chest was closed.

During recovery of each animal from anesthesia, while surface electrogram activity was being monitored for arrhythmias, the iontophoretic subcutaneous electrodes were connected to the constant-current power source and a current of 900 μA was passed for 30 min across the implanted HCM-reservoir device. Following this, the skin over the electrode leads was sutured closed. Two and 4 weeks after implantation of the device, the animals were again anesthetized, and the electrical leads from the device were exposed by a transcutaneous incision. The 900-μA current and blood sampling protocol were repeated as above with monitoring of the surface electrocardiogram activity for arrhythmias. Blood samples from the cephalic vein were taken before implantation and before and after each 30-min/900-μA current protocol. At the end of 4 weeks the animals were sacrificed with an overdose of phenobarbitone and the chest was opened to retrieve the device for explant assessment.

Statistical Methods. Grouped Student t testing was used to compare differences between selected sotalol (coronary and peripheral) levels and between periodic VERP changes. Linear regression analysis was used to correlate *in vitro* steady-state release rates and iontophoretic currents. Linear regression was also used to evaluate the significance of the relationship between initial peak coronary sotalol levels and the iontophoretic current. Data are presented as mean ± SEM.

RESULTS

***In Vitro* Characterization of the Iontophoretic Device.** The *in vitro* iontophoretic delivery of sotalol was found to be modulated for each of the three current protocols, A, B, and C (see above). In protocol A (off/100 μA/off/450 μA/off) the

Downloaded at Palestinian Territory, occupied on December 19, 2021

respective steady-state delivery rates were 0.36/1.09/0.31/4.10/0.38 mg/hr. Similarly, in current protocol B (off/450 μA/off/450 μA/off) steady-state rates were 0.38/3.84/0.45/3.83/0.46 mg/hr, and for protocol C (off/900 μA/off/450 μA/off) the steady-state rates were 0.34/8.28/0.35/4.37/0.43 mg/hr (Fig. 2). The steady-state release rates determined at 100 μA, 450 μA, and 900 μA currents were found to be linear with the current applied (0.9 mg/hr per 100 μA; $r^2 = 0.996$, $P = 0.002$).

Acute Iontophoresis in Dogs. Iontophoresis resulted in current-dependent regional modulation of drug release from the implant in the acute dog studies, as demonstrated by the coronary plasma sotalol levels (Fig. 3) and VERP changes (Table 1). Furthermore, no arrhythmias were noted during these acute protocols, nor was cardiac stimulation noted during iontophoresis. Baseline coronary and peripheral plasma levels demonstrated some initial variability due to the surgical instrumentation and trauma associated with implantation of the iontophoretic reservoir. Nevertheless, the coronary sotalol levels after initial iontophoresis demonstrated phasic changes in response to the current protocols (Fig. 3). The coronary plasma sotalol levels attained in each on current phase were dependent upon the amplitude of the current applied in each protocol. In current protocol A, the current off mean baseline coronary sotalol level was 74 ± 24 ng/ml, while

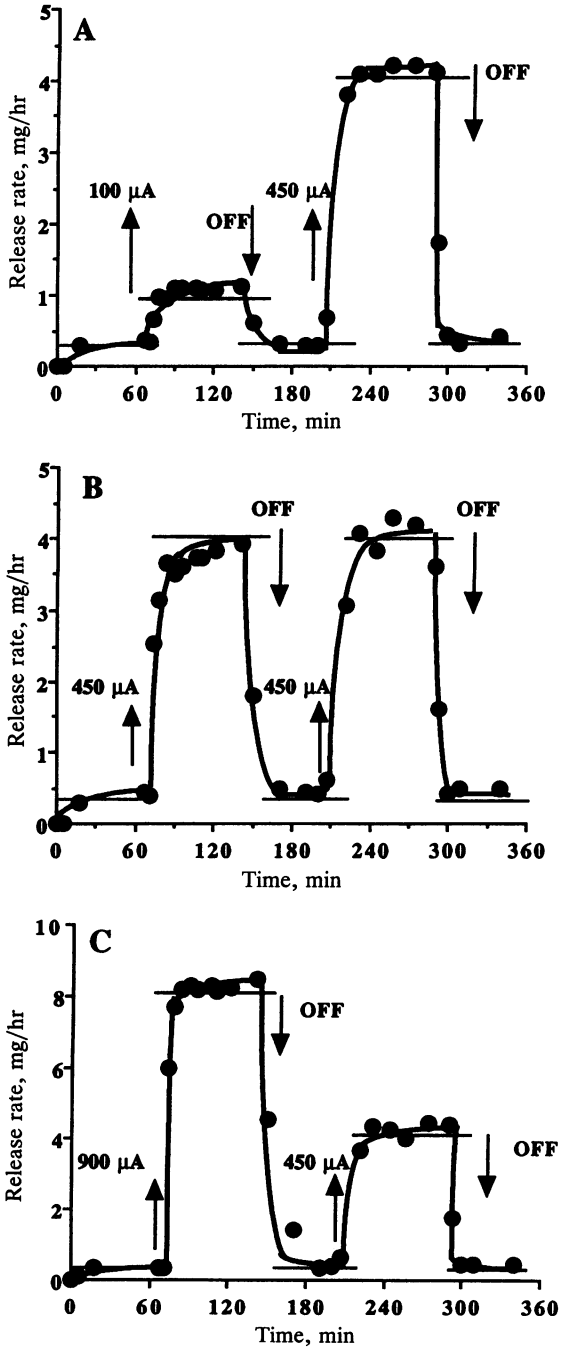

FIG. 2. *In vitro* iontophoretic modulated release rates of sotalol from an implantable HCM-reservoir under three different off and on current protocols. (*A*) Protocol A, off/100 μA/off/450 μA/off. (*B*) Protocol B, off/450 μA/off/450 μA/off. (*C*) Protocol C, off/900 μA/off/450 μA/off. Horizontal lines indicate the delivery rates calculated from Nernst- and Planck-based theory (9).

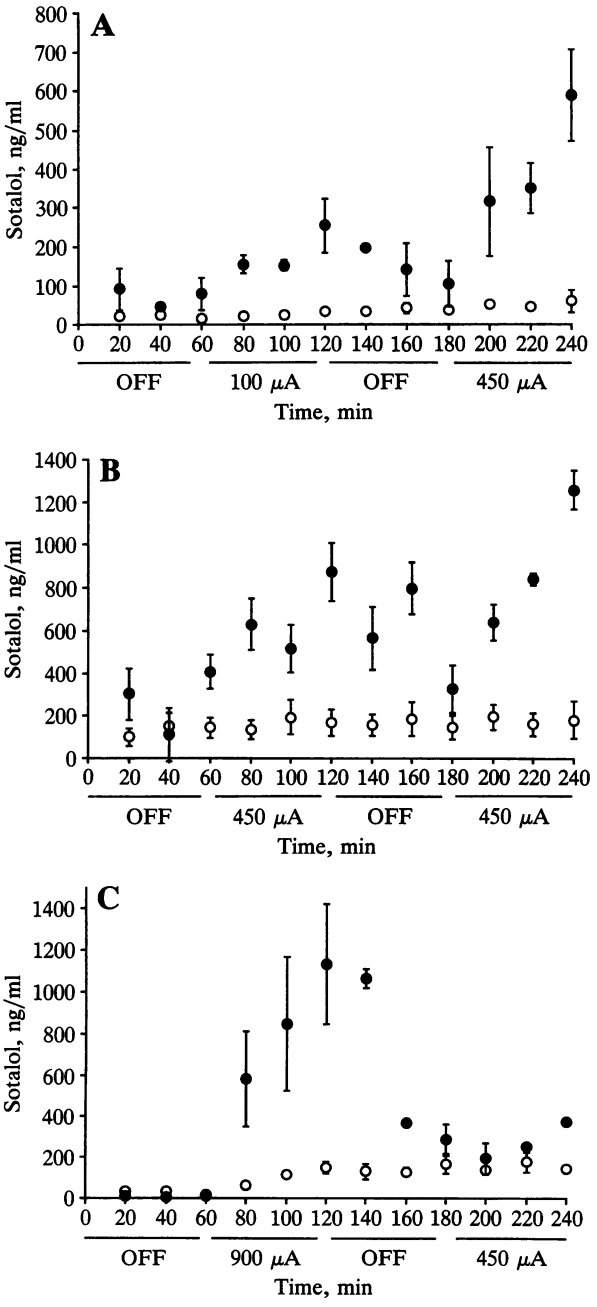

FIG. 3. Changes in the coronary (●) and peripheral (○) plasma sotalol levels with off and on iontophoretic currents in dog experiments with acute current protocols as follows: (*A*) Protocol A. (*B*) Protocol B. (*C*) Protocol C. Each current protocol was carried out in three dogs for a total of nine acute studies. Sotalol levels are represented as mean ± SEM.

Downloaded at Palestinian Territory, occupied on December 19, 2021

Table 1. Changes in VERP due to sotalol administered by iontophoresis

Iontophoretic current protocol	VERP, msec					
	Initial		Period I		Period II	
	Proximal electrode	Distal electrode	Proximal electrode	Distal electrode	Proximal electrode	Distal electrode
A (100 μA/450 μA)	132.0 ± 4.6	126.7 ± 1.7	144.7 ± 3.4	138.7 ± 2.9†	147.3 ± 3.3	141.0 ± 0.5‖
B (450 μA/450 μA)	126.7 ± 1.7	128.0 ± 6.4	134.0 ± 3.0	136.7 ± 2.3	138.7 ± 3.6*	141.0 ± 0.5
C (900 μA/450 μA)	139.3 ± 1.7	137.3 ± 2.3	149.3 ± 2.9*	157.7 ± 2.0¶	159.3 ± 3.3‡	159.0 ± 2.8§

Probabilities, compared with the corresponding initial VERP in all cases: *, $P = 0.04$; †, $P = 0.02$; ‡, $P = 0.006$; §, $P = 0.004$; ¶, $P = 0.003$; ‖, $P = 0.001$.

for 100-μA iontophoretic current the level was 191 ± 30 ng/ml ($P = 0.01, t = -2.9$). In protocol B the mean baseline coronary level was 256 ± 62 ng/ml, while for the 450-μA current the level was 686 ± 86 ng/ml ($P = 0.007, t = -3.5$). In protocol C, mean baseline coronary level was 11 ± 3 ng/ml, while for the 900-μA current the level was 818 ± 162 ng/ml ($P = 0.0005$, $t = -4.6$).

Furthermore, the peak coronary drug levels attained at the end of 1 hr of each current-on phase correlated significantly ($P = 0.002$) with the amplitude of the current applied (Fig. 4). In addition, by 180 min (1 hr after the initial current-off period) peripheral and coronary levels showed no significant differences between current protocols A, B, and C (see Fig. 3). The peripheral plasma sotalol levels measured simultaneously during each of the current protocols were at the lower limits of detection and were less strongly responsive to each current protocol compared with the coronary venous data.

Increases in the VERP measured at the proximal and distal electrodes were in general dependent on the iontophoretic current. Current protocol C involving maximal (900/450-μA) currents demonstrated the greatest changes in VERP at both the proximal and distal electrodes compared with the other protocols. However, significant but lesser increases in VERP were noted with the lower current protocols (Table 1). Furthermore, there were no statistically significant differences between the VERP effects noted at the proximal and distal electrodes, indicating nonlocalization of the pharmacologic effects of regional sotalol over the left ventricle.

Chronic Iontophoresis in Dogs. Current-responsive increases in release kinetics over time (as reflected by the peripheral plasma sotalol levels) were observed on the first day after surgery and 2 and 4 weeks after implantation. No arrhythmia activity was detected during the sotalol-iontophoresis protocols, and cardiac stimulation was not observed during iontophoresis. As shown in Fig. 5, the peripheral sotalol levels increased significantly in response to a 900-μA current passed for 30 min. The decline in peripheral plasma sotalol levels over time (between studies) with the 900-μA current protocol was accounted for by depletion of the drug from the reservoir. Residual drug analysis data from nine dogs showed 52.8% ± 4.8% depletion of the sotalol solution from the devices after 4 weeks. The HCM potentials measured at implantation and at 2 and 4 weeks after implantation were 12 ± 2, 10 ± 2, and 12 ± 2 V, respectively, at 900-μA current. This indicates that the electrical characteristics of the HCM did not change significantly following implantation.

Upon explantation, a fibrous capsule was typically found to have formed over the exterior surface of each reservoir implant. However, no fibrous tissue or thrombus was observed to be present at the interface of the HCM with the left ventricular epicardium. Explant iontophoretic characterization of the HCM-reservoir devices for their *in vitro* release rates when refilled with a fresh sotalol solution revealed that the current-dependent release kinetics were not significantly altered compared with preimplant (3.9 ± 0.2 vs. 3.7 ± 0.3 mg/hr at 450 μA and 0.3 ± 0.1 vs. 0.3 ± 0.1 mg/hr at the off current condition; $n = 9$).

DISCUSSION

This study demonstrated successful regional cardiac drug delivery modulated by iontophoresis. An HCM system was investigated as a rate-limiting barrier for iontophoresis. Current-responsive release kinetics were clearly demonstrated, and the device was well tolerated in a series of animals in acute and chronic studies. Furthermore, the iontophoretic implants were robust and were found to have sustained low power requirements over time.

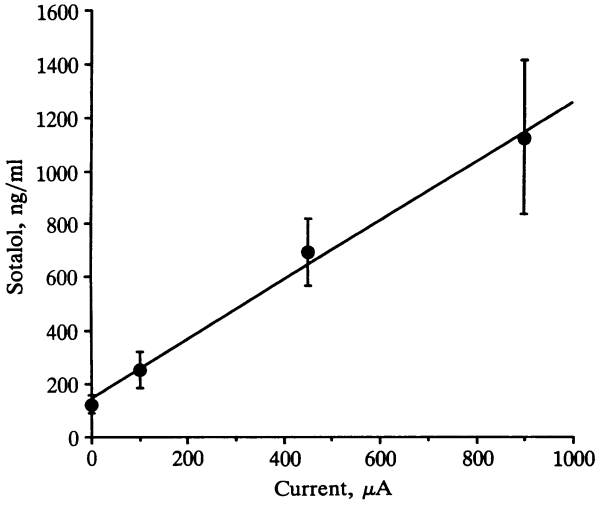

FIG. 4. Relationship between current and the sotalol levels in the dog coronary circulation during acute studies. Levels shown were attained at the end of each hour of the off and on current protocols ($r^2 = 0.995$, $P = 0.002$).

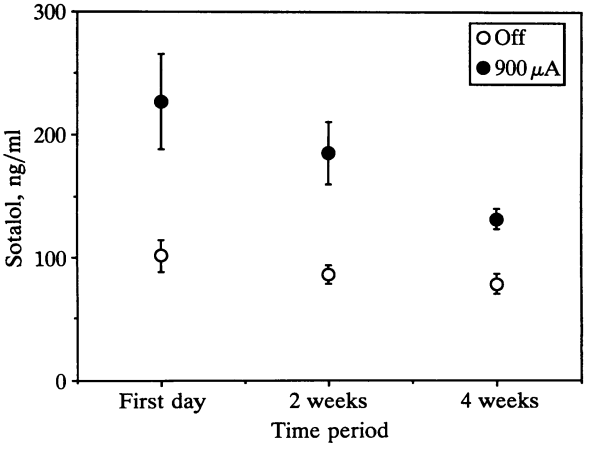

FIG. 5. Changes in the peripheral sotalol levels over time with periodic 900-μA iontophoresis for 30 min in 30-day chronic studies in dogs. For each time point sotalol levels were significantly greater after iontophoresis ($P < 0.02$). Data are represented as mean ± SEM ($n = 9$).

Downloaded at Palestinian Territory, occupied on December 19, 2021

Sotalol Modulation by HCM Iontophoresis *in Vitro*. Our *in vitro* characterization of the HCM iontophoretic membrane demonstrated a linear relationship between current and release rates, and this rate dependence was nearly in agreement with the kinetics predicted from derivations of the integrated Nernst–Planck equations (6–9). Furthermore, the results demonstrated a rapid responsiveness of the release rates to various changes in transmembrane current of the controlled release kinetics, with steady-state release kinetics occurring after 5–10 min in most studies.

***In Vivo* HCM Iontophoresis for Cardiac Drug Administration.** In the acute studies of dogs, coronary plasma sotalol levels reflected the current-dependent responsiveness of the controlled-release kinetics, as in our *in vitro* studies (Fig. 2). Furthermore, the changes in the VERP were dose related in general and were almost of the same magnitude measured at proximal and distal electrode locations. The overall pattern of the increase in the VERP in our acute studies in response to epicardially delivered sotalol was similar to VERP changes noted with sotalol-polyurethane monolithic matrices acutely implanted epicardially in dogs by our group (3).

The potential advantages of the HCM iontophoresis cardiac implants for arrhythmia therapy include the possibilities of feedback regulation of drug delivery rates in response to electrocardiogram changes or other parameters governing arrhythmia therapy. The reservoir-HCM implant used in our long-term implant studies could obviously be refilled to replenish or change drugs. In addition, it may be advantageous to use this approach for the administration of other cardiovascular drugs for various other cardiovascular disease processes (10, 11). Furthermore, our iontophoresis approach involving current passage only across the HCM (and not the myocardium) is advantageous compared with other iontophoresis protocols (12, 13) in which electrical current is passed through cardiovascular tissues, raising the possibility of electrically induced trauma or electrophysiologic stimulation.

Other controlled-release methods, electromagnetism (14) and ultrasound (15), have also been demonstrated to successfully regulate implant drug release kinetics. However, HCM iontophoresis is particularly well suited for long-term and self-contained arrhythmia-related implants, because of the low energy requirements with this form of delivery. Furthermore, HCM iontophoresis offers the possibility of electrical control of both the iontophoresis system and a feedback-related antiarrhythmic device, such as a pacemaker or implantable defibrillator.

The authors thank Mrs. Catherine Wongstrom for her efforts in preparing this manuscript. We also are appreciative of the technical assistance from Ms. Marsha Gallagher. This research was supported in part by grants in aid from the National Heart, Lung and Blood Institute (1R01HL41663) and from the American Heart Association of Michigan (V.L.).

1. Brugada, G. (1988) *Pacing Clin. Electrophysiol.* **11,** 2246–2248.
2. Labhasetwar, V., Kadish, A., Underwood, T., Sirinek, M. & Levy, R. J. (1993) *J. Controlled Release* **23,** 75–86.
3. Labhasetwar, V., Underwood, T., Gallagher, M., Murphy, G., Langberg, J. & Levy, R. J. (1994) *J. Pharm. Sci.* **83,** 157–164.
4. Labhasetwar, V., Underwood, T., Gallagher, M., Langberg, J. & Levy, R. J. (1994) *J. Cardiovasc. Pharmacol.* **24,** 826–840.
5. Siden, R., Kadish, A., Flowers, W., Kutas, L., Bieneman, B. K., DePietro, J., Jenkins, J. P., Gallagher, K. P. & Levy, R. J. (1992) *J. Cardiovasc. Pharmacol.* **19,** 798–809.
6. Schwendeman, S. P., Amidon, G. L. & Levy, R. J. (1993) *Macromolecules* **26,** 2264–2272.
7. Schwendeman, S. P., Amidon, G. L., Meyerhoff, M. E. & Levy, R. J. (1992) *Macromolecules* **25,** 2531–2540.
8. Schwendeman, S. P., Amidon, G. L., Labhasetwar, V. & Levy, R. J. (1995) *J. Pharm. Sci.* **83,** 1482–1494.
9. Schwendeman, S. P., Labhasetwar, V. & Levy, R. J. (1994) *Pharmacol. Res.*, in press.
10. Villa, A. E., Guzman, L. A., Chen, W., Golomb, G., Levy, R. J. & Topol, E. J. (1994) *J. Clin. Invest.* **93,** 1243–1249.
11. Levy, R. J., Wolfrum, J., Schoen, F. J., Hawley, M. A. & Langer, R. (1985) *Science* **228,** 190–192.
12. Fernandez-Ortiz, A., Meyer, B. J., Mailhac, A., Falk, E., Badmon, L., Fallon, J. T., Fuster, V., Chesebro, J. H. & Baddimon, J. J. (1994) *Circulation* **89,** 1518–1522.
13. Avitall, B., Hare, J., Zander, G., Bockoff, C., Tchou, P., Jazayeri, M. & Akhtar, M. (1992) *Circulation* **85,** 1582–1593.
14. Edelman, E. R., Brown, L., Taylor, J. & Langer, R. (1987) *J. Biomed. Mater. Res.* **21,** 339–353.
15. Kost, J., Leong, K. & Langer, R. (1989) *Proc. Natl. Acad. Sci. USA* **86,** 7663–7666.

Downloaded at Palestinian Territory, occupied on December 19, 2021