Iontophoretic Transmyocardial Drug Delivery

A Novel Approach to Antiarrhythmic Drug Therapy

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Background. Antiarrhythmic drugs often fail to achieve therapeutic effects without toxic systemic levels. Direct transport of drugs into the myocardium may circumvent this problem and may also provide new insights into antiarrhythmic drug effects on arrhythmogenic tissues. In a canine model, procainamide (PA) was delivered iontophoretically using pulsed current synchronized with the ventricular depolarization via an implantable defibrillator patch electrode that was modified to contain a 3.6-ml chamber. Myocardial tissue concentrations of PA were evaluated in 7-day myocardial infarcts (n=16) that were exposed to 10 minutes of iontophoretic PA delivery and compared with passive diffusion (n=5) and intravenous (n=16) PA. These dogs were followed for 3 hours. The infarcted tissue PA levels were compared with normal myocardium. Coronary and systemic blood levels of PA, effective refractory period (ERP), diastolic threshold, and efficacy of ventricular tachycardia (VT) suppression were evaluated throughout the follow-up period.

Methods and Results. Three hours after 10 minutes of iontophoretic, passive, and intravenous PA, the epicardial layer concentration in the center of the infarcted zone was 840±853 μg/g, 93±90 μg/g, and 15±8 μg/g of tissue, respectively. In the endocardial layer, the PA concentrations with iontophoresis were 38±57 μg/g and were significantly higher than those achieved with either passive diffusion (4±2 μg/g) or with intravenous delivery (11±5 μg/g) (p<0.05). Epicardial tissue PA concentrations 3 hours after iontophoresis, passive diffusion, and intravenous PA in the normally perfused tissues were 14±13 μg/g, 3±2 μg/g, and 16±8 μg/g of PA, respectively. Venous blood levels were 2±3 μg/ml 3 hours after iontophoresis, 1±1 μg/ml 3 hours after passive PA delivery, and 11±7 μg/ml with intravenous administration (p<0.05 intravenous versus passive and iontophoresis). Iontophoretic delivery of PA resulted in 22±29 msec ERP prolongation intramurally in the infarcted zone with no significant normal tissue ERP prolongation. Passive delivery of PA produced no significant changes in ERP. After intravenous infusion, the ERP in the infarcted zone increased by 35±29 msec and 13±12 msec in the normal tissue. Sustained monomorphic VT was induced in 20 animals. In one of these animals, only nonsustained VT could be induced at baseline; however, after intravenous PA, VT could be induced and remained inducible throughout the 3-hour follow-up period. In the iontophoretic delivery group, PA suppressed VT in all of the animals, with termination time ranging from 20 seconds to 7 minutes. In three cases, sustained monomorphic VT could be induced, two after 60 minutes and one after 120 minutes. However, in seven dogs, VT could not be induced during the 3-hour follow-up period. None of the dogs in which PA was delivered iontophoretically into the infarcted myocardium developed VT that was not induced before delivery of the drug. Intravenous PA administration resulted in VT suppression in one of 10 dogs. In two dogs, VT could not be induced before intravenous infusion of PA. However, after intravenous PA, VT could be induced. Immunohistochemical mapping of the PA within the infarcted tissue revealed transmural PA distribution.

Conclusions. These data show that 1) the delivery of high transmural concentrations of PA directly into infarcted myocardium is both feasible and effective. PA concentrations in the infarcted tissues were significantly above therapeutic levels for over 3 hours after 10 minutes of iontophoretic drug exposure, with only minimal levels detected in the circulation, 2) PA delivery into the infarcted myocardium using iontophoresis is much more effective than either passive diffusion or intravenous administration, and 3) in this model, VT is rapidly suppressed by the iontophoretic delivery of PA into the infarcted area; however, effective refractory period and diastolic threshold did not increase dramatically with iontophoretic PA delivery.

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Key Words • Iontophoresis • Arrhythmia • Procainamide

The poor efficacy of antiarrhythmic agents administered at clinically tolerable doses may in part be related to an inadequate concentration of the drug in the target tissue. Delivery of a drug such as procainamide (PA) directly into an arrhythmogenic substrate using the technique of iontophoresis could lead to high tissue concentrations and avoidance of systemic toxicity.

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Iontophoresis uses electrical current to transport charged molecules into tissue or the blood stream. Presently, this process is used to deliver drugs through the skin. Although the myocardium should provide a much lower resistance to iontophoretic drug transport than the skin, this idea has never been explored in cardiovascular pharmacology. In recent years, implantable devices with direct myocardial electrode patches have increasingly been used to treat ventricular tachycardia (VT) and ventricular fibrillation. These electrode patches could be a convenient way to deliver an antiarrhythmic drug directly into the myocardium by using iontophoresis.

The aim of this study, therefore, was to determine whether iontophoretic transport of PA into infarcted myocardium is technically feasible and effective in suppressing VT in a canine model. Results were compared with intravenous administration and passive diffusion of this drug.

Methods

Drug Delivery System

To develop and test a direct epicardial drug delivery system, a Cardiac Pacemaker Incorporated automatic implantable cardioverter-defibrillator platinum mesh patch electrode was trimmed to 9 cm² and modified to contain a 4-mm-deep chamber that was sealed with dialysis membrane (chamber volume, 3.6 ml). The pore size of the permeable membrane is 400 A, which allowed the PA molecule to pass through the membrane and onto the epicardial surface. The chamber was equipped with ports to allow infusion of the drug (Figure 1). PA hydrochloride at a concentration of 100 mg/ml was the initial prototype drug used to test the efficacy of iontophoretic versus passive and intravenous drug delivery into a 7-day infarct canine model.

PA, supplied at pH 5, is a charged molecule with a molecular weight of 271.79 and is suitable for iontophoretic delivery.¹

Surgical Preparation

Under sterile conditions, 37 male mongrel dogs (weight, 20–25 kg) were premedicated subcutaneously with 2 mg/kg morphine 30 minutes before being anesthetized with 25 mg/kg i.v. pentothal. Anesthesia was maintained with 1–1.5% halothane with 4 l/min O₂. The chest was opened using a small incision at the fourth intercostal space. The left anterior descending coronary artery (LAD) was ligated just proximal to the second diagonal branch. In addition, other small arteries from the apex and lateral wall that feed into the LAD area were also ligated. The chest was repaired, and the animal was allowed to recover for 7 days. After this period, the dogs were anesthetized with pentothal 25 mg/kg and maintained on 1–1.5% halothane with 4 l/min O₂ with the use of a Harvard apparatus respirator. Femoral arterial pressure and surface ECGs were monitored continuously, and blood gases were maintained at physiological range. In the event of blood gas (O₂, CO₂, and pH) deviation from the physiological range, ventilator settings were adjusted, supplemental O₂ was used, and lung atelectasis was minimized. Blood gases were repeated to ensure stability. The heart was exposed through a median sternotomy and suspended in the pericardial cradle. The coronary sinus was cannulated with a 6F catheter, which was placed in the great cardiac vein. The femoral vein was cannulated for venous blood sampling. A 3-mm stainless steel wire electrode was threaded to approximately 4 mm below the epicardial surface in the center of the infarcted zone. Wide margins were allowed for entrance and exit of the wire to prevent overlap between the drug delivery patch (described below) and the myocardial puncture sites. A second wire was placed in the right ventricle away from the infarcted zone. These electrodes were used for the evaluation of the effective refractory period (ERP), end-diastolic threshold (EDT), and the initiation of VT.

A bipolar-ring electrode was sutured to the border of the infarcted zone between the two stimulating electrodes (Figure 1). This electrode permitted recording of discrete signals free of far-field artifact. The recording electrode was connected to a Bloom recording system for monitoring the electrical activity of the heart. A 14-cm² reference electrode for stimulation was imbedded subcutaneously in the hind leg, and a 14-cm² platinum mesh patch electrode was secured to the posterior surface of the heart and was used as a reference electrode for the iontophoretic current. The sinus node was crushed, and the heart was paced at 150 beats per minute using a 2-msec cathodal pulse with an amplitude of twice diastolic threshold. The pacing pulse was delivered to the wire electrodes implanted in either the infarcted or normal tissue (see Figure 1, sites A and B), as were the test stimuli for the determination of the ERP and EDT. The open chest cavity was covered with thick pads to prevent cooling. The drug delivery patch, lined with platinum mesh and equipped with two ports to allow infusion of either the drug or normal saline, was connected to a constant-current pulse generator. The output of the constant-current unit was electrically

Figure 1. Schematic diagram of the instrumented heart. A: Infarcted tissue stimulation electrode embedded 4 mm into the myocardium. B: Normal tissue stimulation electrode. C: Bipolar-ring recording electrode. D: Iontophoresis patch electrode and chamber with inlet and outlet tubing (F,G) for antiarrhythmic drugs. E: Reference patch electrode. F: Infarcted tissue stimulation electrode insertion site outside the margins of the iontophoretic chamber. G: Site of left anterior descending coronary artery ligation. H: Great cardiac vein cannulated with 6F catheter for blood sampling.
isolated to prevent any current loops other than the current between the patches (Figure 1).

The efficacy of iontophoretic PA transport into infarcted myocardial tissue was compared with passive drug diffusion and intravenous administration. For 10 minutes, PA at a concentration of 100 mg/ml was passively exposed to the myocardial surface or was delivered iontophoretically for 10 minutes with 1 mA/cm²–80-msec pulsed current, synchronized with ventricular pacing at 150 pulses per minute. During VT, the iontophoretic pulses were limited to 150 pulses per minute synchronized with the R wave recorded from the ring electrode. The iontophoretic current pulse pathway was between the modified anterior patch containing the drug and the posterior patch as shown in Figure 1. After each of these interventions, the patch containing PA was removed from the heart, and any moisture was blotted from the epicardial surface that had been exposed to the PA. Intravenous PA was infused slowly at a 15-mg/kg loading dose followed by a 0.6-mg/kg/min constant infusion.

**Electrophysiological and Sampling Methods**

Coronary sinus and venous blood samples were taken at 1, 5, 15, 30, 60, 120, and 180 minutes, timed from the beginning of PA exposure. ERP, EDT, and inducibility for arrhythmia were measured before and after PA exposure at the same intervals as blood sampling using the Bloom Associates stimulation system. Ventricular stimulation was performed with cathodal impulses 2 msec in duration at two times diastolic threshold. Two different basic cycle lengths were used: 600 and 400 msec. Up to four premature beats were delivered to the infarcted and noninfarcted zones via electrodes A and B (shown in Figure 1). The initial coupling interval of an extrastimulus was 300 msec, which was decremented by 10-msec intervals until VT was induced or ventricular effective refractory period was achieved. This extrastimulus was then fixed at 10 msec above refractoriness, and an additional premature beat was inserted that was similarly decremented.

By using this stimulation protocol, the inducibility of VT was tested every 30 minutes over a 2-hour period before PA exposure to ensure reproducibility of VT induction in 12 dogs (Table 1) and after PA exposure for 3 hours. Electrical current and saline may cause electrophysiological changes comparable to those seen after PA exposure, and VT induction and stability may change over time. Electrophysiological evaluations were performed in 12 dogs with inducible VT before drug exposure by measuring the ERP, EDT, VT suppression, and changes in VT cycle length. The infarcted epicardium was exposed to a saline-filled drug delivery patch with pH similar to that of the PA (pH 5) for 10 minutes with pulsed iontophoretic current. Drug delivery patch temperature was maintained at the dog heart temperature. Intramyocardial pH was evaluated with a Corning pH/C 107 meter and Microelectrodes Inc. MI-407 miniature needle electrode in four of the dogs. The intramyocardial pH needle electrode was inserted into the

**Study Groups**

Measurements were determined in three groups of dogs. 1) Sixteen dogs that received 15 mg/kg PA i.v. followed by 0.6 mg/kg/min PA infusion: Fifteen were followed for 3 hours and one was followed for 30 minutes. 2) Five dogs in which infarcted epicardial tissue was exposed to PA administered by passive diffusion from the drug delivery patch for 10 minutes: The drug delivery patch was then removed from the heart, and the epicardium was blotted dry. These dogs were followed for 3 hours. 3) Sixteen dogs in which infarcted epicardium was exposed to pulsed-current PA iontophoresis for 10 minutes: The drug delivery patch was then removed from the heart and the epicardium was blotted dry. These dogs were followed for 3 hours.

### Table 1. Reproducibility of Ventricular Tachycardia After Saline Iontophoresis Into the Infarcted Zone and 2-Hour Follow-up Period

<table>
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<th>VT CL</th>
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Mean 1.4 204 187 3 1.4 204 182 3 1.3 205 185 3 1.2 25 28 1
±SD 1.5 27 26 1 1.3 20 28 1 1.2 25 28 1

VT, ventricular tachycardia; EDT, end-diastolic threshold (mA); ERP, effective refractory period (msec); VT CL, ventricular tachycardia cycle length (msec); ES, number of premature stimulations that initiated VT; CONV, mode of VT conversion; ODP, overdrive pacing; DCCV, direct current cardioversion.
myocardium immediately after iontophoretic PA delivery. No measurable pH changes were recorded intramurally under the iontophoretic patch. Although the iontophoretic current could pace the heart, it was synchronized with ventricular systole with a total pulse duration of 80 msec. When appropriately triggered, no arrhythmias were recorded during or after iontophoretic current application.

At the end of the 3-hour observation period, the patches and all other electrodes were removed from the heart, and the heart was removed. The hearts were rinsed in saline, and four transmural punch biopsies traversing the drug-exposed infarcted zone were taken (Figure 2). Two additional biopsies were taken from the site of right ventricular stimulation and the left ventricular free wall. Both of these sites were remote from the drug-exposed zone. Core biopsies were sectioned longitudinally. These sections were used for histology and immunohistochemistry, whereas the remaining core biopsies were divided into three equal segments containing the endocardial, intramural, and epicardial tissues (Figure 2). The right ventricular biopsy was divided into only two segments. From these samples, drug concentrations were measured using high-performance liquid chromatography (HPLC).

Immunohistochemical Analysis

The myocardial biopsies were fixed in 10% buffered formalin for 4–6 hours, processed through a series of graded alcohol solutions to a clearing agent, infiltrated with liquid paraffin, and embedded in paraffin blocks. Four-micrometer sections were placed on 3-aminopropyltriethoxysilane-coated glass microscope slides and air-dried overnight. The polyclonal primary antiserum was prepared by monthly injections of rabbits with PA bovine serum albumin in Freund's complete adjuvant. Both the primary antisera and normal rabbit serum (NRS) were absorbed with dehydrated dog heart powder to block nonspecific binding. Immunohistochemistry was performed using a Fischer Code-on histostainer (Fisher Scientific). The slides were deparaffinized with xylene followed by reagent ethanol. Endogenous peroxidase was eliminated with hydrogen peroxide and methanol. After treatment with 95% ethanol and a water rinse, tissue conditioner (Biomedica) was applied to further block nonspecific binding of either the primary antibody or NRS for 30 minutes at 37°C. Unbound antibody was removed by washing with 1X Biomedica automation buffer. Tissue sections were incubated with the peroxidase-conjugated secondary antibody reagent for 30 minutes at 37°C. After washing to remove excess antibody, chromogenic detection was performed with aminoethyl carbazol substrate, counterstained with hematoxylin, and covered with Crystal mount (Biomedica). Under light microscopy, PA was localized by the presence of red granules. Positive and negative control slides were processed simultaneously. In addition, a section from each tissue block was processed with NRS substituted for the primary antibody. From each biopsy sample, hematoxylin–eosin–stained sections were prepared for histological examination by light microscopy. Serum PA levels were determined by enzyme immunoassay (Syva Emit).

Myocardial Procainamide Level Determination

Fresh canine heart tissue was obtained by cardiac puncture using a 10.5-mm biopsy instrument. The tissue was separated into endocardial, intramural, and epicardial sections and was immediately placed on dry ice. Frozen myocardial biopsies were homogenized (1:5, tissue:water) with a Brinkman Polytron until a uniform suspension was obtained. After centrifugation at 7,000g for 10 minutes, an internal standard consisting of a propyl analogue of PA was added to an aliquot of the supernatant. Samples were applied to an activated Bond Elute C2 solid-phase extraction column and washed with H2O:CH3CN (90:10). PA and internal standard were eluted with 50 mM triethylamine phosphate, pH 3.0:CH3CN (60:40). After filtration, the samples were injected into the HPLC and separated using a 5-μm C8 reverse-phase analytical column and a mobile phase of 50 mM triethylamine phosphate, pH 3.0:CH3CN (83:17) at 1.4 ml/min. A Perkin Elmer fluorescence spectrometer with excitation and emission monochrometers set at 275 nm and 345 nm, respectively, was used for detection. Quantification of PA was performed using a standard curve plotting microgram per milliliter standard versus the ratio of PA to internal standard, using both peak area and peak amplitude measurements. Linear regression constants obtained from standard curves were used to calculate PA concentrations in the myocardial biopsy samples. Blood level analysis was
done using the enzyme multiplication immunoassay technique PA assay by Syva Corporation, Palo Alto, Calif.

Statistical Analysis

One-way analysis of variance technique was used to define the statistical significance of the ERP and EDT changes and myocardial and blood drug concentrations at the different time intervals. Data are presented as mean±SD; results with a value of p<0.05 were considered statistically significant.

Results

The results reported here are based on data collected in the 37 canine experiments. In 12 dogs in which sustained monomorphic VT could be induced with programmed stimulation, the reproducibility of VT induction was followed after 10 minutes of saline iontophoresis every 30 minutes for 2 hours. In 11 dogs, the ERP and EDT were evaluated throughout the 2-hour follow-up period (in dog 8, Table 1, the EDT was above 10 mA). In these dogs, VT morphology, mode of induction, and termination were the same. No statistically significant changes in ERP, EDT, or VT cycle length were observed. In one dog (dog 9, Table 1), the VT could not be induced after saline iontophoresis; however, the same tachycardia was induced 15 minutes later (Table 1).

Tissue Concentration and Distribution of Procainamide After Passive, Iontophoretic, and Intravenous Delivery Into Infarcted Myocardium

Three hours after iontophoretic PA delivery into the infarcted tissue, the concentration of PA was considerably higher than the concentration of PA delivered with passive diffusion from the drug delivery patch or intravenous administration (Figure 3). The greatest amount of drug was retained in the epicardial layer at the center of the infarcted zone (840±853 µg/g of tissue versus 93±90 µg/g with passive diffusion and 15±8 µg/g with intravenous administration), whereas the lowest concentrations were found in the endocardial layer. However, in the center of the infarcted zone, the endocardial layer PA concentrations with iontophoresis were still higher (38±57 µg/g) than those achieved with either passive diffusion (4±2 µg/g) or with intravenous delivery (11±6 µg/g, p<0.05). Passive diffusion showed no significant differences between the normal and infarcted zones in all three layers 3 hours later. However, 3 hours after intravenous PA, the concentration of PA in the normal tissue was higher than in the center of the infarcted zone intramural and endocardial samples. Only iontophoretic PA delivery produced very high concentrations of the drug in the epicardial and intramural layers, which were distributed across the infarcted zone (p<0.05). HPLC determination of PA tissue and serum concentrations showed no shifts in PA retention time, which indicates that by using the HPLC method, no changes in the PA structure occurred after iontophoresis, passive, and intravenous PA delivery.

Coronary Sinus and Venous Procainamide Blood Concentrations

High concentrations of PA were recorded in the coronary sinus (49±33 µg/ml) and venous blood (58±16 µg/ml) immediately after intravenous PA administration. In contrast, iontophoretic delivery resulted in initial high concentrations of PA in the coronary sinus (11±8 µg/ml) but very low concentrations in the venous circulation (0.3±0.3 µg/ml, p<0.0001). Whereas coronary sinus PA concentration slowly decreased after the completion of PA delivery by passive or iontophoretic diffusion, venous PA concentration slowly increased over 30 minutes and remained stable thereafter. After 3 hours, passive diffusion of PA resulted in venous levels of 0.85±0.67 µg/ml (range, 0.3–2 µg/ml); 3 hours after iontophoresis, the venous level was 2.4±3.35 µg/ml (range, 0.52–13.3 µg/ml). In one only of the 16 dogs was the venous blood level at a high therapeutic level, whereas in all other dogs, the maximum level did not exceed 5.3 µg/ml. These levels were recorded with very high infarcted tissue PA concentrations and are significantly lower (p<0.05) than the PA levels in the circulation after intravenous infusion. In contrast to the passive and iontophoretic PA delivery, intravenous administration resulted in a venous blood level of 11.4±6.7 µg/ml (range, 5.1–27.6 µg/ml) (Figure 4).

Electrophysiological Changes

The time course of ERP and EDT values evaluated during the 3-hour monitoring period are shown in Table 2. In the infarcted tissue, iontophoresis and intravenous PA administration resulted in similar ERP prolongation, and there was no statistical difference between these two groups. Iontophoretic PA delivery to the infarcted zone caused no ERP prolongation in the normal tissue. Intravenous PA resulted in a significant prolongation of the ERP in the normal tissue, which is, however, smaller than the prolongation recorded in the infarcted tissue. The EDT rose transiently after iontophoresis, and no other significant changes were noted for either iontophoresis or intravenous delivery. The ERP prolongation after iontophoretic PA delivery was recorded with venous PA levels that were markedly lower than the PA levels that were recorded with intravenous PA infusion.

Suppression of Ventricular Tachycardia

Sixteen dogs received PA iontophoretically. Ten of these dogs had sustained monomorphic VT. Sixteen dogs received PA intravenously, and 10 of these dogs had VT. As shown in Table 3, iontophoretic PA delivery was effective in terminating and preventing the reinduction of VT for up to 3 hours in seven of 10 dogs. In three dogs in which the VT was reinduced, the time of reinduction was 60–120 minutes. The ERP evaluated in the intramural tissue in the center of the infarcted zone did not show consistent ERP prolongation immediately after PA iontophoresis (21±23 msec; range, 0–70 msec with circulating blood level of 2.6±2 µg/ml). The ERP prolongation was more pronounced 3 hours later, with the exception of one dog (30±26 msec; range, 0–90 msec with circulating PA levels of 2.6±1.7 µg/ml). Measurements of the ERP in the intramural tissue
changed little initially and increased as the PA passively diffused deeper into myocardial tissues. Tissue PA levels show wide variations from one dog to another. Low tissue PA levels in the center of the infarct do not translate to ineffective VT suppression. PA venous blood levels were below the therapeutic range. In 10 dogs with VT that received intravenous PA, nine could be reinduced with programmed stimulation after PA infusion. Two dogs with no inducible VT (dogs 2 and 3) and one with nonsustained VT (dog 7) became inducible for sustained VT after intravenous PA. ERP prolongation was noted in all except one dog immediately after intravenous PA (30±15 msec; range, 0–50 msec with PA venous levels of 27.3±13 μg/ml). These changes in ERP were associated with the high circulating drug levels as a result of the bolus effect. ERP prolongation decreased in all the dogs (10±9 msec; range, 0–30 msec as circulating blood PA levels decreased to 13.7 μg/ml) 3 hours later with therapeutic drug levels. In the center of the infarcted zone, epicardial PA tissue levels (20±12 μg/g) were greater than the intramural and endocardial tissue levels (12±8 and 11.5±7 μg/g of tissue, respectively; p<0.05).

None of the dogs in which PA was delivered iontophoretically into the infarcted myocardium developed VT that was otherwise not induced before delivery of the drug. In an additional animal, a hemodynamically stable, sustained monomorphic VT was induced with a cycle length of 200 msec. PA delivered iontophoretically into the infarcted zone successfully terminated the tachycardia after 2 minutes. VT was noninducible with only a trace level of systemic PA (1.3 μg/ml). After 90 minutes, VT could be reinduced. Intravenous PA was then administered, increasing the venous PA level to 26 μg/ml.

Figure 3. Bar graphs show procainamide tissue levels at 3 hours after delivery into the infarcted tissue by passive diffusion (Pass), iontophoretic delivery (Ionto), and intravenous (IV) administration. Note scale differences for the three tissue layers. Epi, epicardium; Intra, intramural; Endo, endocardium.
this high blood level, VT (cycle length, 340 msec) was easily induced throughout the 1-hour follow-up period. However, after reinitiation of iontophoretically delivered PA, VT was again rapidly suppressed.

**Procainamide Tissue Distribution by Immunohistochemical Analysis**

An example of PA distribution in the 7-day infarcted tissue 3 hours after 10 minutes of PA iontophoresis is shown in Figure 5, panel 3. This section demonstrates intense granular cytoplasmic staining and appears similar to the staining seen in normal myocardial cells that were soaked in 100 mg/ml of PA for 24 hours, shown in panel 2 of Figure 5. The control section taken from a normal canine heart that was not exposed to PA shows no such staining (panel 1). In contrast to the iontophoretic zone, the staining intensity in the remote section (shown in panel 4) is considerably less intense. PA staining was noted transmurally within viable cells and included the endocardial surface. Upon histological examination of the hematoxylin–eosin–stained sections, neither passive diffusion nor iontophoresis caused any epicardial tissue injury beyond that which one would expect from a chronically infarcted myocardium.

**Discussion**

Less than 40% of patients with life-threatening VT are treated successfully with antiarrhythmic agents. In 18%, these drugs may be proarrhythmic, and side effects are encountered in 52%. This necessitates the discontinuation of the drugs in 23% of the patients treated with drug therapy. In only 18% of patients with sustained monomorphic VT was the arrhythmia suppressed by intravenous PA or quinidine administered during electrophysiological study. In the same report, ERP prolongation, determined in the right ventricle, was not predictive of the effect of PA on VT. It has been shown that high systemic doses of PA significantly increase the effectiveness of the drug but often cause intolerable side effects. These sobering data suggest
that transportation of the drug by the systemic circulation is not an effective route to suppress VT without the use of toxic drug levels. Furthermore, surgical therapy for VT has been shown to be effective in only 60–70% of patients in whom surgery was attempted.\(^8\)^\(^9\) Poor ventricular function and multiple VT morphologies with diffuse, nondescript infarcts preclude many patients from surgical therapy. Implantable defibrillators do not prevent initiation of the VT, and, as a result, many patients receive frequent multiple shocks, which in turn may lead to further damage to the myocardium.\(^10\) At this time, there is no other effective therapy for these patients. It has been shown that retroperfusion of the infarcted myocardium was considerably more effective in suppressing ventricular arrhythmias in the dog than intravenous PA infusion.\(^11\) However, a chronically implanted, indwelling coronary sinus catheter may cause severe complications.

An alternative approach to this problem would be to deliver locally high concentrations of the effective anti-arrhythmic agents, independent of blood flow, to the areas of injured myocardium containing the arrhythmogenic foci. Drug effectiveness would, therefore, be increased where it is needed most, and systemic drug exposure and its side effects would be minimized. Direct iontophoretic delivery of antiarrhythmic drugs will not result in toxic levels of the drug in the normal myocardium, because the drug will be rapidly removed and diluted by the circulating blood. Furthermore, this method of drug delivery may provide a new insight into the mechanism of proarrhythmia by contrasting the electrophysiological effects of intravenous drug delivery (causing global changes) and iontophoretic delivery (causing local changes). Our data demonstrate that high drug concentrations occur in the infarcted regions of the myocardium where the slow-conducting reentrant circuits are likely to be present.\(^12\)

Levy et al\(^13\) used lidocaine–polyurethane matrixes to passively deliver the drug into normal myocardial tissue. This method was shown to effectively suppress ouabain-induced ventricular arrhythmias. Unfortunately, this technique does not permit periodic replenishment of the drug, nor has it been shown to be effective in suppressing arrhythmias arising from infarcted tissues. In 1964, Folkman and Long\(^14\) proposed the idea that myocardial iontophoresis of triiodothyronine imbedded in Silastic tubes be combined with a pacemaker system for the treatment of complete heart block. These researchers hypothesized that transport of triiodothyronine could increase the local rate of depolarization of myocardial cells and avoid the need for continuous pacing, thus contributing to increased pacemaker life. To date, no data or follow-up publications in the literature have reported on the success of this procedure. Because there are no published data concerning direct myocardial delivery of drugs with iontophoresis, the discussion of factors influencing iontophoretic drug transport summarizes the literature derived from drug delivery into the skin with iontophoresis. These data will serve as a reference and departure point for the discussion of iontophoretic drug transport into the myocardium (presented in the "Appendix"). It is recognized that the epicardial surface is markedly different from the surface of the skin. Such differences include greater electrical impedance of the skin related to the stratum corneum, significantly different active-to-passive flux ratio of drug into the skin, and the low membrane–water partition coefficient for ionic species, which decreases iontophoretic transport of drugs through lipid pathways in the skin when compared with

### Table 2. Effective Refractory Period and End-Diastolic Threshold Before and After Iontophoresis and Intravenous Procainamide Delivery in Infarcted and Normal Tissues

<table>
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<tr>
<th></th>
<th>CTL</th>
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*\(^p<0.01\) vs. CTL.
†\(^p<0.05\) vs. CTL.
‡\(^p<0.01\) ION vs. IV.
§\(^p<0.05\) vs. 15 minutes IV.
transport through an aqueous pathway. Because of the high concentrations of mobile ions in the epicardial surface that come in contact with the membrane of the drug chamber, ions may diffuse into the chamber and are expected to compete with the drug for current.

In this study, the iontophoretic current was set at 1 mA/cm². This current density will cause ventricular depolarization if it is not delivered during the ventricular refractory period. Because iontophoretic drug delivery is a linear function of the intensity of the current and the duration of application, reduction in current density to levels below the ventricular capture threshold will not only decrease the possibility of arrhythmia but also will decrease the amount of drug delivered into the myocardium. However, a proportional increase in the epicardial exposure time to the iontophoretic drug delivery will increase the amount of drug transported and will compensate for the reduction of current. In this study, we did not record any significant local pH changes, nor did we observe any increase in ventricular irritability as a result of local ionic shifts. Furthermore, despite high local PA concentrations recorded in this study, no spontaneous arrhythmia occurred.

The results of PA concentrations recorded in this study show that the epicardial tissue contains the highest concentration of drug and serves as a reservoir of PA, which diffuses down the concentration gradient into the endocardium and from there into the ventricular cavity. In addition, the drug diffuses into peripheral tissues, where it may be cleared by the coronary circulation. The rate of diffusion determines the elimination rate of the drug from the myocardium. The data presented here suggest that the rate of PA elimination from the 7-day infarcted myocardium is much slower than that of normal tissue. This conclusion is supported by the fact that the myocardial PA concentration remained high after the 3-hour follow-up period, and that PA concentration in the blood was low throughout this period. For the antiarrhythmic agent to be effective in suppressing VT, it has to be delivered to the arrhythmogenic substrate in therapeutic concentrations. In this study, no specific attempt was made to map the site of early activation and adjust the site of PA exposure. Furthermore, the drug delivery patch covered only a portion of the infarcted zone. Despite these limitations, in the dogs that developed inducible VT, the VT was suppressed shortly after the initiation of PA iontophoresis. In seven of 10 dogs, the VT was suppressed for the duration of the 3-hour monitoring period after 10 minutes of iontophoretic drug delivery without adverse effects and with subtherapeutic PA levels in the systemic circulation. As shown in Table 3, in three dogs with VT (dogs 2, 7, and 9), iontophoretic delivery of PA resulted in long-term suppression of the VT despite low tissue PA levels in the center of the infarcted zone. In the same dogs, iontophoretic current applied to the saline-filled chamber did not suppress the VT, and the VT was reproducible for 2 hours before iontophoretic

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<td>210</td>
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</table>

PA, procainamide; VT CL, ventricular tachycardia cycle length (msec); ΔERP, change in effective refractory period from before PA effective refractory period (msec); Endo, PA tissue level in the endocardium (µg/g of tissue); Intra, intramyocardium; Epi, epicardium; NI, noninducible; NC, noncapture (infarcted tissue end-diastolic threshold of >10 mA); NSVT, nonsustained ventricular tachycardia.

* Dogs that developed ventricular tachycardia after intravenous PA.
† This dog was followed for 30 minutes.
delivery of PA. These observations may suggest that VT suppression after PA iontophoresis may depend on the concentration of PA at the site of slow conduction that was possibly located at the epicardial surface.

In the human heart, the activation sequence during VT was mapped and correlated with histological studies of the infarcted tissue in the Langendorff-perfused human hearts of transplant recipients. It was concluded that "the location of the tracts is not confined to the subendocardial surface, but many run intramurally or even subepicardially." In the canine VT model, it has been shown that the inducibility of VT peaks after 1 week of infarction after single-stage permanent coronary occlusion. Electrophysiological mapping of these tachycardias revealed intramural and endocardial slow activity in nine of 13 VTs. In the remaining VTs, epicardial reentry was identified, and only two were suppressed by epicardial cooling and cryoablation.

Histological evaluation of the dogs with sustained VT revealed surviving myocardial cells interlaced with acellular tissues. These observations suggest that VT induced in the 7-day infarct in canine heart may originate from different myocardial layers. This is similar to what was observed in the human heart.

One would expect that with high concentrations of PA in the epicardial tissues and to a lesser extent in the intramural and endocardial tissues, the electrophysiological changes should correspond to the PA tissue concentrations; however, that is not the case. At this time, we can only speculate why, and further studies are required to elucidate these findings. Because the PA concentration in the circulation is low, a large tissue-to-circulation gradient is present. The drug diffuses passively from the necrotic tissue in the infarcted zone, which is not well perfused, to islands of myocytes within the infarcted tissue that are capable of responding to the electrical stimulation. These myocytes are alive as a result of blood supply or passive diffusion of oxygen. Any blood supply to these tissues results in removal of the PA. The PA concentration and perhaps the drug electrophysiological effects on the surviving cells within the infarcted zone are influenced by several factors: the concentration gradient between the tissues, the blood flow in the infarcted tissue, and the mobility of the drug. Because the effect of the PA is a function of its concentration, it is conceivable that the electrophysiological effects recorded in this study represent the amount of drug that is present within surviving cells in the infarcted zone. These cells are exposed to much greater levels of PA than is present in the circulation because of their proximity to necrotic tissues that serve as a reservoir of PA, as documented by the HPLC drug tissue levels in the infarcted tissue. However, the PA level in the islands of viable cells is probably not the same level present in necrotic tissues. In addition, it is possible that the electrophysiological effects of PA delivered directly into the infarcted tissue, bypassing the circulation, results in electrophysiological effects that are unlike those recorded with intravenous drug application and yet are effective in suppressing VT. Iontophoretic current may result in PA structure changes leading to diminution of the drug's electrophysiological effects. However, using HPLC analysis, no changes in the elution profile were observed.

Potential Limitations and Future Studies

Large myocardial infarctions that involve the septum may cause VT that is sustained by a deep septal reentrant circuit distant from the iontophoretic site. Such a VT may be resistant to this mode of drug delivery as well as to systemic antiarrhythmic drugs. It is possible that combined systemic and iontophoretic drug application may enhance the suppression of VT that is otherwise resistant to either method alone. However, in all the dogs in which VT was induced, the VT was successfully suppressed by iontophoretic PA delivery for at least 60 minutes, and in seven of 10 dogs, the VT was suppressed for over 3 hours with iontophoretic PA delivery. Furthermore, the center of the drug delivery patch should be placed as closely as possible to the area of the reentrant circuit. For this reason, electrophysiological mapping may provide valuable information for proper patch placement. In addition, it may be necessary to modify several other experimental parameters to achieve optimum therapeutic effect. These additional parameters include drug concentration, duration of drug exposure, patch size and configuration, and type of drug being delivered. Another potential limitation is the possibility that other ionic species with similar charge to that of PA that are used in the preparation of the drug may act as antiarrhythmic when delivered in high concentrations into the infarcted tissues. High PA concentration may cause depression of contractility. In preliminary canine model studies using echocardiographic techniques, iontophoretic PA delivery caused only transient, mild depression of nontransmural 4-week infarcts and did not affect the mechanical function of the normal myocardium. We are currently studying whether PA iontophoresis is as effective in suppressing VT and producing high tissue concentrations in 4-week myocardial infarcts as it was in 7-day infarcts. Furthermore, in contrast to the experiments reported here, the current intensity will be lowered to prevent ventricular capture.
by the iontophoretic pulses, and exposure time will be increased. Chronically implanted drug delivery systems will be used in infarcted dogs so that serial drug testing can be performed to compare drug efficacy and reproducibility of the results.

**Significance**

This work documents for the first time that sustained monomorphic VT caused by myocardial infarction can be suppressed for a significant period of time by epicardial iontophoretic drug delivery. Rapid high concentrations of PA were achieved within the infarcted tissue and sustained even after 3 hours following the removal of the drug delivery patch from the heart. This new approach to drug delivery may be further developed into an implantable drug delivery system capable of recognizing ventricular arrhythmias and containing a subcutaneous pump and chamber that can be replenished through a subcutaneous port. The system may deliver electrical current to a specially designed patch affixed to the surface of the heart directly over the arrhythmogenic site. When spontaneous runs of VT are detected, the antiarrhythmic drug will be pumped into the patch and transported into the myocardium iontophoretically by pulsed electrical current. This system may also be incorporated into the automatic implantable defibrillator, which already has the capability of recognizing ventricular arrhythmias. A system such as this is shown in Figure 6. The design of an implantable system capable of delivering drugs to the arrhythmogenic site may pose a significant challenge. However, given the current technology of implantable pumps and the implantable defibrillator, it is believed that such a system can be successfully developed. This method of drug delivery will minimize the systemic effect of the drug and maximize the effect within the affected myocardium. It will provide a new modality for the treatment of life-threatening arrhythmias that are otherwise refractory to conventional forms of medical and surgical therapy. The potential use of such a drug delivery system extends beyond antiarrhythmic drugs, because its uses can be expanded to deliver inotropic agents such as dobutamine, vasodilators, β-blockers, or any cardioactive agents that can be transported directly into the myocardium passively or iontophoretically. Furthermore, because most of the drug effect is limited to the infarcted tissue, it has the potential of increasing the efficacy of the drugs and may provide valuable insights into the antiarrhythmic and proarhythmic action of antiarrhythmic drugs.

**Conclusions**

This study shows that 1) the delivery of high concentrations of PA directly into infarcted myocardium is both feasible and effective, 2) PA concentrations in the infarcted tissues were significantly above therapeutic levels for over 3 hours after 10 minutes of iontophoretic drug exposure, with only minimal levels detected in the circulation, 3) PA was distributed transmurally within the infarcted tissue, 4) PA delivery into the infarcted myocardium using iontophoresis is much more effective than either passive diffusion or intravenous administration, and 5) in this model, VT is suppressed by the iontophoretic delivery of PA into the infarcted area.

**Appendix**

Factors that influence iontophoretic drug transport include 1) ionization state: The efficacy of drug delivery using iontophoresis depends heavily on the ionization state of the substance to be delivered. Siddiqui et al. have evaluated the effect of iontophoresis of lidocaine through human stratum corneum. Iontophoresis was most effective in the pH range of 3.4–5.2, in which lidocaine is highly ionized. Without iontophoresis, passive lidocaine permeation through the excised human stratum corneum is maximal at pH 9.4 or above, in which lidocaine is mainly nonionized. In this pH range, iontophoretic transport of lidocaine was minimal. 2) Excretaus ions: The presence of ions of like charge in the drug solution decreases the amount of drug transported into the
tissue because these ions compete with the drug for the iontophoretic flux. Small mobile ions can considerably diminish the amount of drug transported into the tissue. It is desirable that more than half of the ion flux be carried by the drug molecule. 3) Ionic strength: It has been shown that an increase in the ionic strength of the solution subjected to iontophoretic current resulted in a reduced iontophoretic transport of the desired ion into the tissue. 4) Concentration: As can be shown by the Nernst-Planck equation, an increase in the concentration of the charged molecule to be delivered by iontophoresis yields a greater concentration of the molecule in the tissue. 5) Current intensity: The amount of drug delivered as a result of iontophoretic current can be described by the Faraday law of electrochemical reaction Q = (tj*i*t)/(z*F) where Q is the amount of drug that is delivered iontophoretically, tj is the transference number that defines the portion of the current that is related to the drug, i is the current in amperes, t is the duration in seconds, z is the absolute value of the valence of the drug ion, and F is the Faraday constant. As shown by this equation, the amount of drug delivered is a linear function of the intensity of the current, the duration of application, and the percent of current carried by the drug ions. It has been shown by several investigators that this relation holds under experimental conditions, and, in a given set of experimental conditions, the transference value is fixed. 6) Polarization: Direct electrical current applied to the skin can cause polarization and possibly skin irritation. Furthermore, the observation that insulin delivery was enhanced by pulsed current suggests that pulsed current may minimize tissue polarization. 7) Shifts in tissue and drug solution pH: Shifts in pH are often noted with the use of metallic electrodes, and such changes can affect the ionization state of the drug. These shifts can be avoided by the use of silver-silver chloride electrodes. Another area of concern involves pH shifts within the tissue, as these changes have been postulated to be associated with tissue injury. These changes are a result of migration of hydronium and hydroxyl ions produced by electrolysis. To avoid such pH changes, Sander son et al have designed electrodes that contain separate buffered electrolyte solutions that use an ion exchange membrane of appropriate polarity. This prevents the flow of electrolyzed ions into the tissue.

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